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Table of Contents

SUMMARY

Acute Toxicity

In a comparative study in which Ni and Ni salts were administered i.v. to mice, Selivanova et al. (684) found that the soluble sulfate and nitrate salts were the most toxic, LD_{100} 4.8 mg/kg Ni for both, metallic Ni was least toxic, 450 mg/kg and the less soluble salt, nickel carbonate was intermediate in toxicity, 380 mg/kg Ni.

The LD_{50} of $Ni(CO)_4$ administered to rats by four routes was reported by Hackett and Sunderman (242) as i.v., 22 ± 1.1 mg Ni; s.c. 21 ± 4.2 mg Ni; i.p. 13 ± 1.4 mg Ni and inhalation, 0.12 mg Ni/rat. (See Acute Toxicity Tables, Table 7 , page 14 for more data.)

Short-Term Toxicity

Weber and Reid (846) found that when two toxic levels of Ni; 1100 ppm (157 mg/kg/day) and 1600 ppm (228.5 mg/kg/day) were added as the acetate salt to the basal diet of young mice, there was a significant growth reduction at the higher level. When mature mice kept on the dietary Ni supplements were bred, there was a significant decrease of pups born ($P < 0.05$) to those fed the higher level.

When young rats were fed Ni-supplemented diets at lower levels (100, 50 and 25 mg/100 g basal diet) Phatak and Patwardhan (591) found no significant growth rate differences at eight weeks and no differences in reproduction. The test materials were Ni soaps, catalyst and Ni carbonate.

Chernen'kii and Smirnova (119) concluded after p.o. administration to rats of $NiCl_2$ at Ni concentrations of 0.06, 0.12 and 0.3 mg/kg for thirteen days that Ni may not be innocuous for animals.

Itskova et al. (303) administered aqueous solutions of varying concentrations of two Ni salts ($NiCl_2 \cdot 6H_2O$ and $NiSO_4 \cdot 7H_2O$) daily by stomach tube to groups of white rats in two experiments; one for 40 days (5 mg/kg and 20 mg/kg Ni as $NiCl_2 \cdot 6H_2O$) and one for 7 months (0.0005 mg/kg, 0.005 mg/kg, 0.05 mg/kg; 0.5 mg/kg and 5.0 mg/kg). After 40 days , half the animals in the first experiment were given doses equivalent to the LD_{50} (105 mg/kg for male and 129 mg/kg for female). From the lack of mortality, the authors concluded Ni does not have a cumulative effect. The experimental animals in the second experiment gained less weight than the controls and noticeable changes in the mucuous membranes of the upper section of the small intestine were found.

Schroeder and Mitchener (672) found that when Ni was given in the drinking water to rats at doses which do not interfere with growth and survival (5ppm Ni equivalent to 0.5 mg/kg/day as a soluble salt), reproduction was affected so that at each generation (of three) litter size decreased. Developing males in utero were more vulnerable to Ni than developing females. The authors concluded that for certain trace elements this kind of reproductive study was more sensitive for detecting toxicity than life-time feeding.

Weber and Reid (847) evaluated the effects of high levels of Ni (0, 100, 300, 500, 700, 900, 1100 and 1300 ppm equivalent to 12.5, 37.5, 62.5, 87.5, 112.5 and 137.5 mg/kg/day) as the acetate or sulfate when added to the basal diet of four-week old chicks and fed ad libitum. It was found that both Ni salts caused a significant growth depression; the amount of ingested

Ni controlled good consumption, as well as a reduction in nitrogen retention.

When rabbits were administered p.o. 5 to 20 mg/kg pulverized Ni daily for nine months, Tardivel et al. (767) found that despite the lack of any clinical evidence of intoxication, 90% of the animals showed a leucocytosis with lymphocytosis. At higher daily doses, 100 to 500 mg/kg pure Ni powder, the animals still maintained an outward appearance of health but also showed a leucocytosis. Electrophoretic study of the blood serum showed changes affecting the globulin distribution. The authors attributed the hematological and electrophoretic changes to the administered Ni.

O'Dell et al. (550) fed high levels (0, 62.5, 250 and 1000 ppm equivalent to 1, 4 and 15.5 mg/kg/day) of Ni (as $NiCO_3$) to calves for eight weeks. A significant reduction in growth rate and feed consumption occurred at dietary levels of 250 ppm. Histopathologically, kidney was the only tissue damaged, the damage increasing in severity with increasing dietary Ni level and culminating in pyelonephritis.

Phatak and Patwardhan (591) found no effect of Ni on growth, health, levels of food intake, hemoglobin or blood counts in adult monkeys fed Ni in the form of carbonate, soaps of mixed fatty acids of groundnut oil, and Ni catalyst at dietary levels of 100, 50 and 25 mg Ni per 100 g mixture, for six months.

Brandes (087) reported the case of a chemist who died after brief exposure to $Ni(CO)_4$. Analysis gave a strong Ni reaction in lung tissue and a weaker one in brain.

Herring et al. (268) reviewed the evidence for Ni as a probable cause of carcinoma of the respiratory tract among Ni refinery workers. They also cited Ni as an important cause of dermatitis. They did not believe available data in 1960 was sufficient to relate Ni to blood disease.

Long-Term Toxicity

Schroeder et al. (674) in a continuation of their studies on the effects of trace metals when fed to mice in concentrations duplicating human lifetime accumulations, gave mice 5 ppm Ni (as the acetate salt) for 36 months at which time all the animals had died. After one year, both sexes weighed less than controls (4 to 13%); also longevity was decreased. The authors concluded that Ni had an "innate toxicity" to mice at tissue levels within the human range.

Sunderman and Donnelly (729) found that when rats inhaled 0.03 mg/l $Ni(CO)_4$ vapor 30 minutes/day, 3 times/week for their lifetime, that their mortality after two years was three times greater than the controls, and over the three-year period of the study, their mean weight was also reduced.

Schroeder et al. (675) gave 5 ppm Ni in drinking water to rats for life. There was no significant difference in life spans of experimental and control rats. At 18 months, Ni-fed rats were smaller than controls but up to six months Ni apparently enhanced growth. The authors concluded that at this level Ni was not toxic to rats.

Special Studies

Gilman (215) found that two Ni compounds, Ni_3S_2 and NiO, isolated from refinery dust were tumorigenic when given i.m. to two different strains of mice. A strain difference

was noted, with C_3H more refractory than Swiss mice, based on percent tumor response. All the tumors were sarcomas.

Hueper (285) duplicated the conditions of Ni workers who develop respiratory cancer by exposing rats over 21 months to 15 mg powdered Ni/m^3 air six hours/day four to five days/week. The benign hyperplastic adenomatoid proliferations which developed in the rats' lungs were attributed by the author to reaction of the respiratory tract to inhaled Ni.

Sunderman et al. (734) showed that inhalation of $Ni(CO)_4$ could cause pulmonary cancer in the resistant rat lung, by exposing rats to $Ni(CO)_4$ vapor at concentrations of 0.03 and 0.06 mg/liter three times/week for one year and at 0.25 mg/liter once.

Gilman (215) found that when suspensions of three powdered Ni compounds ($NiSO_4 \cdot 6H_2O$, NiO, and Ni_3S_2) were administered i.m. to rats, tumors at the injection site developed in 89% of Ni_3S_2-treated, 66% of NiO-treated and none of $NiSO_4 \cdot 6H_2O$-treated animals.

Sunderman and Donnelly (729) found that when rats, a species generally considered resistant to lung cancer, were exposed to $Ni(CO)_4$ vapor, six of 89 animals surviving beyond the two-year latent period developed primary pulmonary carcinoma with metastases. They noted that the amount of Ni capable of inducing lung cancer in the rat is comparable to the amount inhaled by smokers, from less than 15 cigarettes/day for one year.

Practically all the guinea pigs exposed to Ni powder (by inhalation) six hours/day four to five days/week for 21 months, developed adenomatoid proliferations in

the lungs, approaching in some the character of microsarcomas.

Sunderman and Sunderman (730) pointed out that in a burning cigarette all the reactants and reaction conditions are present which can lead to the formation of $Ni(CO)_4$ and that the amount of inhaled Ni (in $Ni(CO)_4$) which caused rats to develop lung cancer was one-third the amount inhaled by heavy smokers (two packs/day/year).

D'Alonzo, et al. (144) in reviewing the literature on acute myocardial infarction, found that Ni was the metal which showed the most significant elevation in the blood serum.

Fregert and Horsman (200) found that women were more allergic to Ni than men on the basis of both patch and intracutaneous tests. Ni in stainless steel was observed to be less allergenic than in plated articles.

Breakdown

Lich (433) reported that when Ni salts were ingested they largely combined with food proteins forming insoluble compounds excreted in the feces. When in excess or when the milieu was hyperacidic, they passed into the bloodstream.

Absorption and Distribution

Selivanova et al. (684) found that when finely dispersed metallic Ni was administered either i.v. or p.o. to mice, rats and rabbits, there was a preferential uptake of Ni by the lungs. Ni was also found in the kidneys, liver, lungs and spleen. The distribution of Ni via p.o. administration differed from that via i.v. administration.

Wase et al. (840) using the isotope ^{63}Ni confirmed Selivanova and coworkers (684) finding that in mice the lungs retained the highest amount of Ni. Ni^{2+} was observed to be widely distributed (kidney, lung, plasma

the most; brain and muscle the least) and rapidly eliminated.

Schroeder et al. (674) found moderate increases in Ni content in kidney, liver, heart, lung and spleen of mice given 5 ppm Ni in drinking water for life, as compared with controls.

Phatak and Patwardhan (591) found that with rats Ni retained in the mother's body after ingesting diets supplemented with 50 or 100 mg/100 g basal diet for about six months, could be transferred to offspring.

O'Dell et al. (552) concluded after feeding lactating cows 50 and 250 ppm Ni with their diet ration, that no appreciable amount of Ni was added to the Ni content of the milk.

D'Alonzo and Pell (143) found abnormally elevated plasma Ni levels in 19 out of 20 myocardial infarction patients.

Metabolism and Excretion

Wase et al. (840) using ^{63}Ni found that with mice in the first eight hours most of the ^{63}Ni was excreted in the feces with urinary excretion reaching a maximum at four hours.

Selivanova et al. (684) found that when rats and rabbits were injected i.v. with $NiSO_4$, Ni excretion peaked on the seventh day after injection and by the tenth day, no Ni was excreted. The amount excreted in the feces was 400 to 600% larger than in the urine. With p.o. administration (50 to 1200 mg/kg metallic Ni), most was unabsorbed and was excreted in the feces.

Caujolle and Canal (113) concluded after $NiCl_2$ i.v. injection to chloralosed dogs with choledocal fistulas that biliary excretion of Ni was minimal.

The main route for Ni excretion in adult humans reported by Kent and McCance (342) was in the urine. This was brought into question by Kincaid (360) who reported a study in which most of the Ni ingested was found in the feces and almost none in the urine. Also, the values for Ni concentrations in urine reported by Kent and McCance (342) were higher than those found by Kincaid (360).

Effects on Enzymes and Other Parameters

Nickel ion (Ni^{2+}) was found to increase the activities of arginase (Hellerman and Perkins (260) of oxalacetic carboxylase (Speck, 713) and in excess, of alkaline phosphatase (Cormane et al. 134).

Nickel ion (Ni^{2+}) was found to inhibit the activity of pancreatic RNase (Roth, 631). Weber and Reid (846) reported that when Ni^{2+} (as the acetate) was fed to mice there was a decrease in the activity of the enzymes, malic dehydrogenase (from kidney homogenate), NADH cytochrome C reductase, cytochrome oxidase and isocitric dehydrogenase (from liver homogenate). The authors pointed out that liver and kidney are the organs where Ni is known to concentrate. At doses of 5 and 0.5 mg/kg Ni p.o. daily to rats, there was a reduction in the activities of alkaline phosphatase and enterokinase in the intestinal contents and mucous membrane scrapings (Itskova et al. 303). Forbes and Smith (193) reported that Ni salts had a marked inhibitory effect on acid production by saliva containing either glucose or sucrose.

Wacker and Vallee (833) found that Ni was present in significant concentration in RNA preparations from phylogenetically diverse sources. Sunderman et al. (733) reported that following exposure of rats to $Ni(CO)_4$, Ni bound to lung and liver RNA was increased.

Drug Interaction

Griffith et al. (229) found that the toxic effects of Ni (as the sulfate) administered p.o. or i.p. to rats were largely neutralized by the simultaneous or separate i.p. administration of cysteine.

Kincaid et al. (360) found that i.m. administration of dimercaprol (BAL) to rats exposed to $Ni(CO)_4$ increased the LD_{50} of $Ni(CO)_4$ by a factor of about 2. Subsequently, Sunderman and Kincaid (731) used BAL to treat 32 persons poisoned by exposure to $Ni(CO)_4$. An increased excretion of Ni in the urine and a marked decrease in Ni concentrations in the blood followed BAL administration. The authors believed the BAL therapy to be beneficial.

Two investigations of the protective effect of $CaNa_2$ EDTA produced conflicting results. West and Sunderman (854) did not find protection against the toxic effects of either inhaled $Ni(CO)_4$ or i.p. Ni nitrate when $CaNa_2$ EDTA was administered in dosages of 100 to 500 mg/kg BW to mice, rats and rabbits. Kocher et al. (376), however, found that when Ca Na_2 EDTA was administered i.p. to mice (at three different dosages) simultaneously with 100 mg/kg Ni sulfate, there was a significant ($P < 0.01$) protective effect at all dosages. Both research groups agreed in finding that $CaNa_2$EDTA had no significant effect on the amount of Ni excreted in the urine.

Consumer Exposure

The average daily intake of Ni from the diet was estimated as 300 to 600 µg (Schroeder et al. 673). A few prepared foods were found to have unusually high Ni values from contamination by processing in Ni vessels (673). Milk pasteurized in Ni vessels was reported (Pratt, 607) to contain 15 ppm Ni as compared with no Ni in milk pasteurized in glass. The significance of

metallic Ni contamination in oils and fats hydrogenated using Ni catalysts was raised by Mastromatteo (479).

Apples sprayed with $NiCl_2$ were found to contain Ni residues at harvest of 125 to 199 µg/10 apples (Stewart and Ross, 722). Sunderman and Sunderman (730) estimated that a person inhaling the mainstream smoke from two cigarette packs/day for one year would inhale 5400 µg Ni, an amount three times the quantity found to be carcinogenic to rats.

Urban air contaminated with Ni (largely from industrial sources with a small amount from motor vehicles) was estimated to range from 0.075 to 3.0 µg based on a respiratory volume of 15 m^3/day. The presence of Ni in the water supply from industrial and natural sources has been found by analysis of water supply systems throughout the United States of America to exceed three times the recommended drinking water standards limit of 0.005 mg/l (766) in a total of 282 of these systems.

Chemical Information

Nickel

I. Nomenclature

A. Common names: none

B. Chemical names: Nickel

C. Trade names: none

D. Chemical Abstracts Service Unique Registry Number: 7440-02-0

II. Empirical Formula

Ni

III. Structural Formula

None.

IV. Atomic Weight: 58.71

V. Specifications

Not available.

VI. Description

A. General characteristics

Hard, ductile ferromagnetic metal with a lustrous white color.

B. Physical properties

Nickel crystallizes[1] in face-centered cubes. It is not affected by water; is slowly attacked by dilute HCl or H_2SO_4 and readily attacked by HNO_3. It is not attacked by fused alkali hydroxides, M. pt. 1455°; B. pt. 3075°; density 8.90.

C. Stability in containers; stable in air at ordinary temperatures.

Nickel Carbonyl

I. Nomenclature

A. Common names: none

B. Chemical names: nickel carbonyl, nickel tetracarbonyl

C. Trade names: none

D. Chemical Abstracts Service Unique Registry Number: 13463393

II. Empirical Formula

C_4O_4Ni

III. Structural Formula

$Ni(CO)_4$

IV. Molecular Weight: 170.73

V. Specifications

Not available.

VI. Description

A. General characteristics

Poisonous, yellow, volatile liquid.

B. Physical properties

Density 71.318; B. pt. 43°; solidif. -25°. Soluble in about 5000 parts air-free water; soluble in alcohol; benzene, chloroform, acetone, and carbon tetrachloride.

C. Stability in containers: Oxidizes in the air, explodes at about 60°.

Nickel Sulfate

I. Nomenclature

A. Common names: Nickel sulfate (anhydrous); Nickel sulfate hexahydrate Nickel sulfate heptahydrate.

B. Chemical names: Sulfuric acid, nickel (2+) salt (1:1); Sulfuric acid, nickel (2+) salt (1:1) hexahydrate; Sulfuric acid, nickel (2+) salt (1:1) heptahydrate.

C. Trade names: none

D. Chemical Abstracts Service Unique Registry Number: 9786814 (anhydrous); 977004-33-3 (hexahydrate)

II. Empirical Formula

O_4SNi (anhydrous)

$O_4SNI \cdot 6H_2O$ (hexahydrate)

$O_4SNi \cdot 7H_2O$ (heptahydrate)

III. Structural Formula

$NiSO_4$ (anhydrous)

$NiSO_4 \cdot 6H_2O$

$NiSO_4 \cdot 7H_2O$

IV. Molecular Weight

154.85 (anhydrous)

262.85 (hexahydrate)

280.85 (heptahydrate)

V. Specifications

Not available.

VI. Description

A. General characteristics

Emerald green, transparent crystals; sweet astringent taste (hexahydrate). The anhydrous compound is greenish-yellow.

B. Physical properties

M. pt. about 100°; soluble in 1.4 parts water; sparingly soluble in alcohol, more in methanol. The aqueous solution is acidic, pH about 4.5.

C. Stability in containers: Somewhat efflorescent (hexahydrate).

VII. Analytical Methods

The analytical methods for Ni are divided into two groups; methods for analyzing Ni in foods and methods for analyzing Ni in biological materials. The types of methods with the materials analyzed are listed below. For details of each method see the original paper which is reproduced in full in Volumes 3,4 of this monograph.

A. Determination of Ni in foods and beverages

1. Spectrochemical
   a. Oils, fats and related substances (548 and 549)
2. Colorimetric
   a. Beers (724)
   b. Malt beverages (340)
3. Spectrophotometric using dimethylglyoxime
   a. Whiskey (612)
   b. Wheat bran, feed and flour (272)
4. Paper chromatography
   a. Foodstuffs; cereals, oats, fishmeal, meat and bonemeal (133)
5. Thin-layer chromatography
   a. Cereal (201)
6. Atomic absorption spectrophotometry
   a. Beer (203)
   b. Wines (493)
   c. Fruit juices and carbonated beverages (492)
   d. Edible fats (610)
7. Activation analysis
   a. Lipids in marine and vegetable oils (452)

B. Determination of Ni in biological materials

1. Spectrophotometry
   a. Human blood (126)
   b. Urine and blood (359)
   c. Serum (740)
2. Spectrochemical
   a. Human plasma and red cells (564)
3. Ultraviolet spectrophotometry
   a. RNA (736)

4. Dimethylglyoxime reagent
    a. Skin (123)
5. Atomic absorption spectrometry
    a. Urine, RNA and serum proteins (738)
    b. Serum and urine (540)
    c. Lungs (326)
6. Circular thin-layer chromatography
    a. Blood and tissue (248)

VIII. Occurrence

A. Plants

Nickel is almost ubiquitous in vegetation and vegetable products, both edible and manufactured. Several whole grains and legumes contain high concentrations (Schroeder et al., 673). As can be seen in Tables 1 and 2, most whole grains have considerable amounts with the largest concentration in buckwheat, rye, oats, corn, rice and one wheat. There was less in milled products indicating concentration in the germ. The exceptions were Japanese wheat and flour. Legumes, tea and cocoa also contain fairly large amounts. There was not a single American vegetable found to be without Ni but two of four fruits were relatively low. Spices and herbal drugs also have been found to contain Ni, as much as 0.014 percent in Strychnos Ignatii beans for example (Monier-Williams, 509).

B. Animals

The amounts of Ni in various tissues of domestic and wild animals are shown in Table 3. Animal products for foods are relatively low in Ni as can be seen in Table 1 (Schroeder et al., 673). Nickel found in milk apparently comes from contamination by the milking machine (Archibald, 017).

The occurrence of nickel in various human tissues by area is shown in Table 4 . Its occurrence in 1,154 samples of eleven tissues was found to be: bone, 5%; liver, 25%; larynx, 31%; kidney, 33%; heart, 42%; trachea, 49%; aorta, 49%; lung, 56%; intestines and skins, 87%.

C. Synthetics

The Ni content of a number of materials is shown in Table 5 . It seems to be relatively ubiquitous, particularly in wood products. A number of alloys and steels also contain Ni such as stainless steel.

D. Natural inorganic sources

Nickel constitutes about 0.016% of the earth crust in igneous rock. The largest source of the metal is from mixed sulfide ores containing pentlandite ($NiFeS_2$), (Mastromatteo, 479).

Certain soils have been found to be high in Ni (Baumslag and Keen, 044 and Monier-Williams, 509). In a survey conducted by the U.S. Public Health Service, Ni was found in river water 17 times out of 51 locations on 17 major U.S. rivers (Schroeder et al., 673).

Table 1

Nickel in Food (673)

Sample	µg per g (wet weight)	µg per 100 g	µg per 100 calories*
Condiments			
Salt, table	0.35	---	--
Pepper, black	3.93	---	--
Baking powder	13.40	--	---
Sugar, cane	0.03	3	1
Yeast, dry active	0.48	--	--
Cinnamon	0.74	--	--
Nutmeg	1.17	--	--
Allspice	0.79	--	--
Bay leaves	0.88	--	--
Cloves, whole	0.10	--	--
Sea food			
Oysters, fresh	1.50	150	300
Clams, fresh	0.58	58	121
Scallops, fresh frozen	0.04	4	4
Lobster, claw meat	0.66	66	55
Shrimp, fresh frozen	0.03	3	3
Crabmeat, canned	0.03	3	2
Anchovies, canned	0.72	72	36
Sardines, canned	0.21	21	7
Kippered herring, canned	1.70	170	85
Haddock, frozen	0.05	5	7
Swordfish, frozen	0.02	2	2
Meats			
Lamb chop	0.0	--	--
Pork chop	0.02	2	1
Pork chop	0.0	--	--
Beef, chuck	0.0	--	--
Beef, round	0.0	--	--
Beef, marrow	0.22	22	6
Gelatin	4.50	450	173
Egg, whole	0.03	3	2
Grains			
Wheat, winter, seed	0.16	16	5
Wheat, Japanese	0.0	--	--
Wheat, Japanese	0.0	--	--
Wheat flour, Japanese	0.0	--	--
Wheat flour, all-purpose	0.54	54	15
Wheat flour, all-purpose	0.30	30	8
Wheat, crushed, Vermont	0.75	75	21
Bread, whole-wheat, stone-ground	1.33	133	53
Wheatena	0.0	--	--

*Calorie values from McCance, R.A. and Widdowson, E.M.: The Chemical Composition of Foods, Chemical Publishing, Brooklyn, 1947.

Table 1 (cont.)

Sample	µg per g (wet weight)	µg per 100 g	µg per 100 calories*
Grains (cont.)			
Wheaties	3.00	300	75
All-bran cereal	0.74	74	25
Grapenuts cereal	0.13	13	4
Buckwheat, seed	6.45	645	194
Rye, seed	2.70	270	80
Oats, seed	2.60	260	65
Oats, seed	1.71	171	43
Oats, precooked, quick	2.35	235	59
Corn, frozen, fresh	0.70	70	20
Corn meal, New Hampshire	0.0	--	--
Corn oil	0.0	--	--
Rice, Japanese, polished	0.50	50	14
Rice, Japanese, unpolished	1.80	180	50
Rice Japanese, polished (204) samples	0.65	65	19
Rice, American, polished	0.47	47	131
Rice, puffed	0.30	30	10
Vegetable shortening, hydrogenated	1.14	114	13
Vegetables			
Potato, raw	0.56	56	61
Peas, fresh frozen	0.30	30	47
Peas, canned	0.46	46	54
Peas, split, dried	1.66	166	55
Beans, string, frozen	0.65	65	930
Beans, string, canned	0.17	17	189
Beans, Navy, dried	1.59	159	52
Beans, yellow-eye, dried	0.69	69	23
Beans, red kidney, dried	2.59	259	100
Spinach, fresh	0.35	35	135
Celery, fresh	0.37	37	411
Beet greens	1.94	194	1763
Swiss chard, organic	0.71	71	260
Escarole, fresh	0.27	27	245
Chicory, fresh	0.55	55	611
Lettuce, garden, organic	1.14	114	1364
Lettuce, head	0.14	14	127
Kale, organic	1.12	112	728
Kohlrabi, leaves, organic	0.47	47	235
Cabbage, white	0.32	32	160
Cabbage, white	0.14	14	70
Cabbage, red	0.24	24	120
Cauliflower leaves	0.19	19	173
Broccoli, fresh, frozen	0.33	33	235
Tomato, fresh	0.03	3	2
Tomato juice, canned	0.05	5	4
Apple, raw	0.0	--	--

Table 1 (cont.)

Sample	mg per g (wet weight)	mg per 100 g	mg per 100 calories*
Vegetables (cont.)			
Apple, raw	0.08	8	18
Banana	0.34	34	50
Pear	0.20	20	50
Fluids			
Milk, whole, fresh	0.0	--	--
Milk, evaporated	0.03	3	2
Milk, evaporated	0.03	3	2
Milk, dry, skim packaged	0.0	--	--
Milk, dry, skim, bulk	0.0	--	---
Tea, Orange Pekoe	7.60	--	--
Cocoa	5.00	500	111
Cola	0.0	--	--
Ginger ale	5/1	--	--
Cider	550/1	55	122
Cider vinegar	315/1	32	--
Beer, canned	10/1	1	2
Mineral water, bottled, Arkansas	12.5/1	1	--
Cigarettes, whole, filtered	0.0	--	--
Animal food			
Poultry wheat	0.11	41	12
Dog food, commercial	2.09	209	51
Rat diet, commercial	3.33	333	88
Rat food (rye, milk, corn oil)	0.20-0.68	20-68	5-17

Table 2.

Nickel in Vegetation(673)

Sample	µg/g (wet weight)
Apple leaves, wild (§1)	1·96
Apple twigs (§1)	1·87
Apple bark (§1)	5·92
Apple leaves, wild (§2)	0·76
Apple twigs (§2)	0·24
Apple (§2)	0·47
Apple leaves, wild (§3)	3·01
Apple twigs (§3)	1·40
Apple (§3)	0·31
Hemlock needles, wild	0·97
twigs	0·03
bark	0·00
Spruce needles, wild	1·69
twigs	1·31
Pine needles, wild	2·44
twigs	0·92
Elm, section 1865–1870, urban	0·10
1900–1910	0·00
1940–1947	0·00
1956–1960	1·15
bark and cambium	0·56
Sawdust, pine	0·65
Wood shavings, soft wood	0·32
Sumac berries	1·10
Peat moss, sphagnum	0·62
Sea weed, floating	0·75
Cow manure, fresh	0·75
Phosphate, rock, Tennessee	33·00
Fertilizer, 0-10-5	14·60
Fertilizer, 0-20-0 phosphate	5·38

Table 3

Nickel in Animal Tissues (673)

Sample	µg/g (wet weight)	
Kidney		
Robin	1·66	
Ruffed grouse	4·96	
Red squirrel, male	0·0	
Red squirrel, female	0·0	
Gray squirrel, male	3·19	
Rabbit, wild	0·0	
Rabbit, wild	0·08	
Deer	0·0	
Deer	2·9	
Deer	0·0	
Deer	0·0	
Deer	0·0	
Deer	0·0	
Deer	0·0	
Deer	1·73	
Deer	0·66	Spectrographic
Deer	0·52	Spectrographic
Deer	<0·16	Spectrographic
Deer	0·0	Spectrographic
Beef	0·66	
Pork	1·0	
Pork	3·4	
Pork	0·0	
Human, mean	<0·09	[12]
Liver		
Salmon, 1 year old	0·28	
Salmon, 4+years old	0·14	
Robin	0·91	
Ruffed grouse	2·42	
Ruffed grouse	1·11	
Red squirrel, female	0·0	
Red squirrel, male	0·0	
Gray squirrel, male	1·51	
Rabbit, wild	2·33	
Deer (§3)	2·5	
Deer (§2)	0·0	
Deer (§4)	0·0	
Deer (§5)	0·0	
Human, mean	<0·11	[12]
Heart		
Gray squirrel	3·67	
Human, mean	<0·12	[12]
Bone		
Beef	0·58	
Muscle		
Lamb	0·0	
Pork	0·0	
Beef	0·0	
Human, mean	<0·11	[12]
Aorta		
Human, aged 82	0·9	
Human, mean	<0·15	[12]

Table 4

Nickel in American Tissues By Area (From Tipton et al. [5–9]) (673)

City of origin	Date†	No. samples*	No. positive	%	No. trace	Total %	Kidney and liver %
Miami, Florida	2/28/57	387	18	4·6	2	5·2	0·0
Denver	3/12/56	268	27	10·1	2	10·8	4·2
Dallas	2/28/57	370	38	10·2	9	12·7	5·5
Baltimore	11/11/57	414	87	21·0	17	25·1	59·2
Richmond, Va.	8/25/59	391	64	16·7	45	28·0	26·4
Seattle–Tacoma	10/6/58	296	94	31·7	10	35·2	26·9
New York–Chicago	12/10/54	233	172	74·0	3	75·0	69·0

Limit of sensitivity of method, 5 p.p.m. ash

*Excluding intestine
†Reported

Table 5

Nickel in Miscellaneous Material (673)

Sample	μg/g (wet weight)
Paper towel	1·43
Paper, excelsior, white	2·07
Paper, newsprint, new	0·64
Paper, building	0·06
Miracle wood	0·40
Plastic wood	0·08
Cellophane excelsior, white	19·50
Polyurethane foam	3·42
Scotch tape, black	6·67
Scotch tape, glass fibre	12·22
Cork, rubber (A. H. Thomas)	1·88
Shellac	0·05
Varnish	0·18

BIOLOGICAL DATA

I. Acute Toxicity

A. Mice

1. Kincaid et al. (359) reported the LD_{50} value for mice (weight, strain, sex and number not given) exposed for 30 minutes to nickel carbonyl ($Ni(CO)_4$) vapor in air to be 10 ppm by volume.

2. Petherick and Singer (586) gave a single s.c. injection of nickel sulfate ($NiSO_4$) to mice (20 g, number, strain and sex not given). The LD_{100} was found to be 0.5 mg/20 g BW (25 mg/kg BW).

3. Kincaid et al. (360) exposed a total of 118 albino mice to $Ni(CO)_4$ vapor for a single 30-minute period (See Table 6). Death, when it occurred, was usually two or three days after exposure. The LD_{50} was computed by the probit method of Miller and Tainter (Miller, L.C., and Tainter, M.L., Estimation of the ED_{50} and Its Error by Means of Logarithmic-Probit Graph Paper, Proc. Soc. Exper. Biol. and Med. 57:261-264, 1944). The LD_{50} was 0.0067 mg/liter (S.E. $\pm$ 0.0003 mg/liter).

Table 6

Estimation of LD_{50} for Mice Exposed to Nickel Carbonyl for Thirty Minutes (360)

	Animals		
Dose, Mg. per Liter	Exposed	Dead	Probit
0.0155.	12	0	(2.98)
0.0465.	15	2	3.89
0.056	10	3	4.48
0.062	29	10	4.60
0.070	20	10	5.00
0.078	22	12	5.11
0.090	10	10	(6.96

Acute Toxicity Table 7

Nickel and Nickel Compounds

(Nickel Sodium EDTA, Nickel Acetate, Nickelocene, Nickel Oxide and Nickel Chloride)

Substance	Animal	Sex & No.	Route	Dosage	Measurement	Reference/ Bibliography No.
$NiNa_2EDTA$ (118.2 mg Ni)	Mice	—	i.p.	1243.6	LD_{50}	376
Nickel Acetate $[Ni(C_2H_3O_2)_2]$	Rats	—	i.p.	35	LD_{50}	246
Nickelocene	Rats	—	i.p.	50	LD_{50}	246
NiO	Cats	—	i.v.	10	LD_{100}	433
NiO	Dogs	—	i.v.	7	LD_{100}	433
$NiCl_2 \cdot 6H_2O$	Rats	M	p.o.	105 (ionic Ni)	LD_{50}	303
$NiCl_2 \cdot 6H_2O$	Rats	F	p.o.	129 (ionic Ni)	LD_{50}	303
$NiCl_2 \cdot 6H_2O$	Dogs	—	i.v.	40 - 80	LD_{100}	433
$NiCl_2 \cdot 6H_2O$	Dogs	—	i.v.	10 - 20	LD_{100}	433

Acute Toxicity Table (cont'd)

Nickel and Nickel Compounds -- Nickel Carbonyl

Substance	Animal	Sex & No.	Route	Dosage	Measurement	Reference/ Bibliography No.
$Ni(CO)_4$	Mice	--	Inhalation	10 ppm by volume	LD_{50}	359
$Ni(CO)_4$	Mice	20	Inhalation	0.067 mg/liter (s.e. $\pm$0.003 mg/liter)	LD_{50}	360
$Ni(CO)_4$	Rats	M	i.v.	22 mg Ni	LD_{50}	243
$Ni(CO)_4$	Rats	M	i.v.	66 mg Ni	LD_{100}	243
$Ni(CO)_4$	Rats	--	Inhalation	35 ppm by volume	LD_{50}	359
$Ni(CO)_4$	Rats	75	Inhalation	0.24 mg/liter	LD_{50}	360
$Ni(CO)_4$	Rats	40 M	i.v.	22 $\pm$1.1 mg Ni	LD_{50}	242
$Ni(CO)_4$	Rats	40 M	s.c.	21 $\pm$4.2 mg Ni	LD_{50}	212
$Ni(CO)_4$	Rats	40 M	i.p.	13 $\pm$1.4 mg Ni	LD_{50}	242
$Ni(CO)_4$	Rats	40 M	Inhalation (40 ml/min ventilation volume)	0.12 mg Ni/rat	LD_{50}	242
$Ni(CO)_4$	Cats	--	Inhalation	270 ppm by volume	LD_{50}	359
$Ni(CO)_4$	Cats	--	Inhalation	1.9 mg/liter	LD_{50}	360

Acute Toxicity Table (cont'd)

Nickel and Nickel Compounds

(Nickel Sulfate - Nickel Carbonate - Nickel Nitrate)

Substance	Animal	Sex & No.	Route	Dosage	Measurement	Reference/ Bibliography No.
$NiSO_4 \cdot 6H_2O$	Mice	--	s.c.	25	LD_{100}	586
$NiSO_4$ (7.8 mg Ni)	Mice	--	i.p. (10% solution)	37.56	LD_{50}	376
$NiSO_4$	Mice	45	i.v.	4.8 mg/kg Ni	LD_{100} (inst.)	684
$NiSO_4 \cdot 6H_2O$	Guinea Pigs	--	s.c.	62	LD_{100}	433
$NiSO_4 \cdot 7H_2O$	Guinea Pigs	5	s.c.	100	LD_{100} (1 hr.)	064
$NiSO_4 \cdot 7H_2O$	Rabbits	5	s.c.	100	LD_{100} (1 hr.)	064
$NiSO_4 \cdot 6H_2O$	Rabbits	--	s.c.	500 - 1000	LD_{100}	433
$NiSO_4 \cdot 6H_2O$	Dogs	--	p.o.	500	LD_{100}	433
$NiSO_4 \cdot 6H_2O$	Dogs	--	s.c.	500 - 1000	LD_{100}	433
Nickel Carbonate $Ni_2(OH)_2CO_3$	Mice	10	i.v.	380 mg/kg Ni	LD_{100} (2nd to 10th day)	684
$Ni(NO_3)_2$	Mice	45	i.v.	4.8 mg/kg Ni	LD_{100} (inst.)	684

Acute Toxicity Table (cont'd)

Nickel and Nickel Compounds -- Metallic Ni

Substance	Animal	Sex & No.	Route	Dosage	Measurement	Reference/ Bibliography No.
Metallic Ni (0.19μ diam.)	Mice	45	i.v. (single injection)	450	LD_{100}	684
Metallic Ni (0.19μ diam.)	Mice	80	i.v. (repeated injection)	600	LD_{100}	684
Metallic Ni (0.19μ diam.)	Mice	70	p.o.	940	LD_{50} (3 to 5 days)	684
Metallic Ni (0.19μ diam.)	Rats	55	i.v. (repeated injection)	600	LD_{100}	684
Metallic Ni (0.19μ diam.)	Rats	55	p.o.	780	LD_{50} (3 to 5 days)	684
Metallic Ni (0.19μ diam.)	Rabbits	15	i.v. (repeated injection)	250	LD_{100}	433
Colloidal Ni	Dogs	--	i.v. (single injection)	100	LD_{100}	433

4. Kŏcher et al. (376) determined the i.p. LD_{50} for $NiSO_4$ and $NiNa_2$ EDTA (9.8% Ni content) with white mice (no details given). The animals were observed for a 10-day period. The LD_{50} for i.p. administration of a 10% solution of $NiSO_4$ was found to be 37.56 mg/kg (7.85 mg Ni) and for a 10% solution of $NiNa_2$ EDTA was found to be 1243.6 mg/kg (118.2 mg Ni).

5. Selivanova et al. (684) compared the acute toxicity of metallic Ni (0.19μ diam.) with Ni in three compounds: two soluble salts, nickel sulfate and nitrate and one less soluble, nickel carbonate, using 145 white mice. The materials were administered in a single i.v. injection. The results are summarized in Table 8. The results showed that the soluble salts were the most toxic, the metallic Ni the least toxic, with the slightly soluble salt showing an intermediate toxicity.

In a second series of experiments, 80 white mice were given i.v. injections of a suspension of metallic Ni (0.19μ diam.) in distilled water at doses from 10 to 600 mg/kg daily for five days. The results are summarized in Table 9. The minimum lethal dose was found to be 100 and the LD_{100} 600 mg/kg. At the largest doses (500-600 mg/kg), there were pronounced toxic effects: sluggishness, thirst, labored breathing, raised body temperatures, albumin and sugar in urine. Death occurred between 5 to 15 days. Body weight loss was correlated with dose size. Animals not dying never fully recovered. The most notable pathological findings were lesions of the respiratory organs with other visceral disorders such as hyperemia and edema.

In a third series of experiments, 70 white mice were administered 50 to 1200 mg/kg finely dispersed metallic Ni p.o. The observed dose effects were:

a) Up to 100 mg/kg, no significant effect.
b) 200 to 400 mg/kg, sluggishness and loss of weight with no change in body temperature.
c) 500 mg/kg was minimum lethal dose.
d) LD_{50} was 940 mg/kg with death occurring within 3 to 5 days.

The stomach and intestine were found to be hyperemic and the mesenteric blood vessels dilated.

The authors concluded from the similarity between the minimum and LD_{100} doses for metallic Ni by single and repeated injections that, unlike the soluble salts, metallic Ni has cumulative properties.

Table 8. Comparative Toxicity of Different Nickel Compounds Following a Single Intravenous Injection of White Mice (684)

Nickel Compound	Number of Animals	Minimum Lethal Dose of Nickel (in mg/kg) in Metal Equivalent	Time of Death	Absolute Lethal Dose (in mg/kg) in Metal Equivalent	Time of Death
Metallic Nickel (Particle Diameter 0.19 μ)	45	50	7th Day	450	5 to 15 days
$Ni_2(OH)_2CO_3$	10		---	380	2 to 10 days
$NiSO_4$	45	2.9	Immediately After Injection	4.8	Immediately After Injection
$Ni(NO_3)_2$	45	2.9	Immediately After Injection	4.8	Immediately After Injection

Table 9

Survival Rate of Animals After Repeated Intravenous Injection of Metallic Nickel (Particle Diameter 0.19μ) (684)

Animals	Total Dose (in mg/kg)	Number of Experimental Animals	Of These		Time of Death (in days)												
			Survived	Died	1 Day	2 Days	3 days	4 days	5 days	6 days	7 days	8 days	9 days	10 days	12 days	15 days	22nd and Later
Rats	600	10	0	10	—	—	1	—	5	1	1	1	—	—	1	—	—
Mice	600	10	0	10	—	—	—	2	3	1	1	2	—	—	—	1	—
Rats	500	5	1	4	—	—	—	—	1	1	1	—	—	—	—	—	1
Mice	500	10	1	9	—	—	—	2	2	—	1	1	—	2	—	1	—
Rats	400	5	2	3	—	—	—	—	—	1	1	—	—	—	—	1	2
Mice	400	10	2	8	—	—	—	2	1	1	—	1	—	1	—	—	2
Rats	300	5	2	3	—	—	—	—	2	1	—	—	—	—	—	—	—
Mice	300	10	10	0	—	—	—	—	—	—	—	—	—	—	—	—	—
Rabbits	250	5	0	5	—	—	—	—		—	—	—	—	—	—	—	—
Rats	200	5	2	3	2	2	—	—	—	1	—	1	1	—	—	—	—
Mice	200	10	8	2	—	—	—	—	—	—	—	—	—	1	—	—	1
Rabbits	150	5	1	4	—	—	—	—	3	—	—	—	1	—	—	—	—
Rats	100	5	4	1	—	—	—	—	—	1	—	—	—	—	—	—	—
Mice	100	10	9	1	—	—	—	—	—	—	—	—	—	—	—	—	1
Rabbits	50	5	2	3	—	—	—	—	2	—	—	—	—	—	—	—	1
Rats	50	5	4	1	—	—	—	—	—	1	—	—	—	—	—	—	—
Mice	50	10	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rats	25	5	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Mice	25	10	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rats	10	10	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—

B. Rats

1. Hackett and Sunderman, Jr. (243) injected $Ni(CO)_4$ into the tail vein of male, Sprague-Dawley rats (120 - 150 g). The LD_{50} dosage was equivalent to 22 mg Ni/kg BW and the LD_{100} dosage was equivalent to 66 mg Ni/kg BW.

The rats developed severe respiratory symptoms. At the LD_{50} level, deaths occurred on the third to fifth days. At the LD_{100} level, all died by the end of the third day. Mild central congestion of the livers on the second to fourth days after injection was seen by gross and histologic examinations. Electron microscopic examination of the hepatic parenchymal cells revealed diffuse dilatation of rough endoplasmic reticulum.

2. Kincaid et al. (359) reported the LD_{50} value for rats (no details given) by inhalation of $Ni(CO)_4$ vapor in air for 30 minutes to be 35 ppm by volume.

3. Kincaid et al. (360) exposed a total of 75 Wistar strain albino rats to $Ni(CO)_4$ vapor for a single 30-minute period (see Table 10). As with mice (see Section A3 above) when death occurred it was usually two or three days after exposure. (For probit method used to compute LD_{50} value, see Section A3 above.) The LD_{50} was found to be 0.24 mg/liter.

Table 10

Estimation of LD_{50} for Rats Exposed to
Nickel Carbonyl Vapor for Thirty Minutes (360)

	Animals		
Dose, mg. per Liter	Exposed	Dead	Probit
0.17	6	0	(3.27)
0.20	18	9	5.00
0.38	21	17	5.88
0.45	18	15	5.97
0.50	12	12	(6.75)

4. Hackett and Sunderman, Jr. (242) reported LD_{50} values of $Ni(CO)_4$ (expressed as mg Ni/100 g) administered via various routes to male Sprague-Dawley rats (100 - 125 g, 40 per route). These values, computed by the probit method described in Section A3 above, were: i.v. 2.2 $\pm$ 0.11; s.c. 2.1 $\pm$ 0.42; i.p. 1.3 $\pm$ 0.14; inhalation (assuming ventilation volume of 40 ml/min) 0.12 mg Ni/rat.

The acute clinical and pathological reactions to injections of $Ni(CO)_4$ by parenteral routes were observed to develop primarily in the lungs and to a lesser degree in the liver. The reactions resembled those previously observed following inhalation of $Ni(CO)_4$. The pulmonary parenchyma was found to be the target regardless of route of administration.

5. Haro and Furst (246) reported the i.p. LD_{50} values for nickelous acetate in trioctanoin administered i.m. to Fischer-344 rats (no details given) as 35 mg/kg and that of nickelocene similarly administered as 50 mg/kg.

6. Itskova et al. (303) administered an aqueous solution of $NiCl_2 \cdot 6H_2O$ (1 ml/100 g) by stomach probe to white rats (M and F, 150 - 170 g). The LD_{50} (for ionic Ni) was found to be 105 mg/kg for males and 129 mg/kg for females. At these doses, the observed symptoms were: depression of the nervous system, heightened motor activity followed by normalization, edema of mucous membranes of mouth and nose, viscous transparent excretions from the mouth cavity, hyperemia of the nose and cochlea and epiphora. Diarrhea and bloody discharges from the nose were seen in a majority of the rats. Death occurred between four and seven hours after administration of the nickel salt.

Other acute symptoms, in addition to the ones described above, were observed at the following dosages:

a) Higher than 250 mg/kg: animals showed strongly pronounced adynamia and areflexia.

b) 172 - 222 mg/kg: immediate strong excitement and heightened motor activity followed in 20 to 40 minutes by a depression of the nervous system.

c) 98 - 148 mg/kg: same as for (b) with exception that motor activity returned to normal.

d) 49 - 73 mg/kg: all symptoms noted above, except less pronounced.

e) 25 mg/kg: no symptoms of acute intoxication.

7. Selivanova et al. (684) administered a suspension of metallic Ni (0.19μ diam.) in distilled water i.v. to 55 rats in doses from 10 to 600 mg/kg daily for five days. The results are summarized in Table 9. The minimum lethal dose was found to be 50 mg/kg and the LD_{100} 600 mg/kg. (For clinical results, see page 18, this Section A5).

The relation of weight loss to dose size in rats was:

a) 20% of initial weight on fifth day after 500 mg/kg.

b) 17% after 200 mg/kg

c) 10% after 50 mg/kg. (See Figure 1)

Other observations were: (These also apply to mice and rabbits.)

a) Increase in skin capillary permeability related to dose size -- the larger thc dose, the earlier the increase and the more pronounced.

b) Trachea and large bronchi were hyperemic in animals dying between third and eighth day.

c) Marked perivascular edema, hyperplasia of peribronchial lymphoid tissue and signs of bronchial-desquamative pneumonia.

When 50 to 1200 mg/kg were administered p.o. to 55 rats; the minimum lethal dose was found to be the same for rats as mice,-- 500 mg/kg and the LD_{100} 780 mg/kg. (See page 18, Section A5 for further observations.)

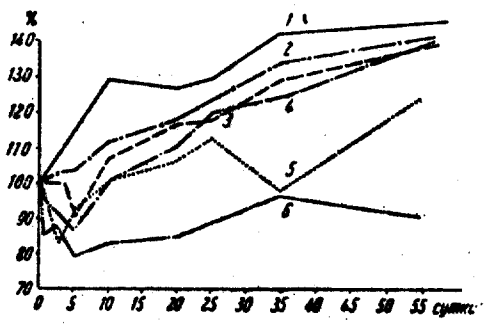

Figure 1. Change in weight of rats after repeated intravenous injection of metallic nickel (mean data for each group of animals).
1 - control; 2 - 25 mg/kg; 3 - 50 mg/kg; 4 - 100 mg/kg;
5 - 200 mg/kg; 6 - 500 mg/kg. (684)

C. Guinea Pigs

1. Bertrand and Serbescu (064) reported that death occurred in about one hour when five guinea pigs (average weight 350 g) were injected s.c. (abdominal skin) with 100 mg/kg $NiSO_4 \cdot 7H_2O$ dissolved in redistilled water.

2. Lich (433) reported that when guinea pigs (no details given) were injected s.c. with $NiSO_4.6H_2O$, the LD_{100} was 62 mg/kg.

D. Rabbits

1. Bertrand and Serbescu (064) reported that death occurred in about one hour when five rabbits average weight 2300 g) were injected s.c. (abdominal skin) with 100 mg/kg $NiSO_4 \cdot 7H_2O$ dissolved in redistilled water.

2. Lich (933) reported that when rabbits (no details given) were injected s.c. with $NiSO_4 \cdot 6H_2O$, the LD_{100} was 500 to 1000 mg/kg.

Lich also reported that the LD_{100} for "soluble nickel salts" administered s.c. to rabbits (no details given) was 7 to 8 mg/kg. At autopsy, such changes as edema, hemorrhages and degeneration of the cardiac muscles, the brain, lungs, liver and kidneys were observed.

3. Selivanova et al. (684) administered a suspension of metallic Ni (0.19μ diam.) in distilled water at doses from 10 to 600 mg/kg i.v. daily for five days. (The results are summarized in Table 9.) The LD_{100} was considerably lower than that found in the same experiment for mice and rats (see this Section, page 18, A5, and page 23, B7) from which the authors concluded that rabbits were the most sensitive to metallic Ni of the three tested species.

E. Cats

1. Kincaid et al. (359) reported the LD_{50} value for cats (no details given) exposed for 30 minutes to $Ni(CO)_4$ vapor in air to be 270 ppm by volume.

2. Lich (433) reported the LD_{100} for s.c. administration to cats (no details given) of the "soluble nickel salts" to be 9 to 16 mg/kg. The same alterations were noted on autopsy as reported for rabbits in Section D2 above.

The same author reported the LD_{100} for i.v. administration to cats of nickel oxide to be 10 mg/kg.

3. Kincaid et al. (360) exposed a total of 12 domestic cats (no details given) to $Ni(CO)_4$ vapor for a single 30-minute period (see Table 11). An LD_{50} value of 1.9 mg/liter was selected by the authors as reasonable after inspection of the data.

Table 11

Exposure of Cats to Nickel Carbonyl Vapor for Thirty Minutes (360)

Dose, Mg. per Liter	Animals		Time of Death After Exposure, Hr.
	Exposed	Dead	
0.19	1	0	...
0.50	1	0	...
1.24	1	1	216
1.94	2	0	...
2.00	3	3	96, 56, 142
2.11	3	3	96, 36, 72
2.43	1	1	40

F. Dogs

1. Lich (433) reported that oral "high doses of metallic derivative of nickel" caused gastrointestinal irritation with vomiting and diarrhea. The LD_{100} for dogs (no details given) was found to be 500 mg (no other details given).

The LD_{100} for i.v. administration of nickel chloride ($NiCl_2 \cdot 6H_2O$) was found to be 40 to 80 mg/kg.

The LD_{100} for i.v. administration of nickel oxide (NiO) was reported as 7 mg/kg.

The LD_{100} for s.c. administration of $NiSO_4 \cdot 6H_2O$ was reported as 500 to 1000 mg/kg.

Dogs were also reported to succumb after i.v. injection of a single dose of 100 mg of colloidal nickel or 200 mg of nickel chloride (no other details were given).

2. Caujolle (111) reported that he and coworkers had found the LD_{100} for i.v. injections of nickel chloride to dogs to be "as low as 20 and 10 mg/kg". There were marked histological liver and kidney lesions.

3. Caujolle and Canal (112) concluded from their experiments that nickel has a "fairly high toxicity". Death was caused quite rapidly with i.v. doses to dogs of 10 to 20 mg/kg.

II. Short term Toxicity

A. In Vitro

In 1951, White and Munns (857) examined the toxic action toward yeast growth of a number of metals, including nickel, used in the brewing or yeast industries.

Yeast growth was carried out in aerated synthetic wort. A requisite amount of nickel was added as a soluble salt. Yeast crops were assayed in the standard way after 24-hour growth.

The results placed nickel, a metal which may be used in the manufacture of modern brewery equipment, in the second or "moderately poisonous" group of metals tested.

The results were expressed as:

a) Ppm of Ni required to reduce yeast growth to 9.7 g, which is half the control yield: 83 ppm.

b) Ppm of Ni required to completely inhibit yeast growth: approximately 185 ppm.

c) A direct "poisoning capacity" of Ni to yeast (this arbitrary scale is described in the original paper): 15.0.

The authors concluded that nickel could, in exponentially-fed operations, cause poisoning of the yeast.

B. Plants

In 1931, Mokragnatz (507) studied the effect of Ni on the growth of Aspergillus niger.

Aspergillus spores were grown on Raulin's liquid (without zinc sulfate) for four days at 34°C, then dried and weighed. Twenty experiments in which nickel sulfate in various concentrations was added to the medium were carried out along with several controls. The summary of the data from representative series is shown in Tables 12-16.

Nickel was found to favor the development of Aspergillus. The favorable effect begins to appear at $\frac{1}{50,000}$ Ni concentration reaching a maximum at $\frac{1}{15,000}$ Ni At $\frac{1}{7,500}$ Ni there is a decrease in recovered weight, and $\frac{1}{3,000}$ Ni prevents mycelium growth almost completely.

Table 12. Effect of Ni on Growth of Aspergillus niger (507)

	Dry weight recovered in grams
Control culture	0.670 g
Culture in presence of $\frac{1}{500,000}$ Ni	0.712 g
Culture in presence of $\frac{1}{100,000}$ Ni	0.776 g
Culture in presence of $\frac{1}{50,000}$ Ni	0.840 g
Culture in presence of $\frac{1}{25,000}$ Ni	0.926 g
Culture in presence of $\frac{1}{15,000}$ Ni	0.997 g
Culture in presence of $\frac{1}{10,000}$ Ni	0.936 g

Coefficient of utility (for the optimal concentration): 1.48

Table 13. Effect of Ni on Growth of Aspergillus niger (507)

Control culture	0.410 g
Culture in the presence of $\frac{1}{50,000}$ Ni	0.610 g
Culture in the presence of $\frac{1}{20,000}$ Ni	0.687 g
Culture in the presence of $\frac{1}{15,000}$ Ni	0.830 g

Coefficient of utility (for the optimal concentration): 2.02

Table 14. Effect of Ni on Growth of Aspergillus niger (507)

Control culture	0.700 g
Culture in the presence of $\frac{1}{150,000}$ Ni	0.825 g
Culture in the presence of $\frac{1}{15,000}$ Ni	1.497 g
Culture in the presence of $\frac{1}{3,000}$ Ni	0.08 g

Coefficient of utility (for the optimal concentration): 2.13.

Table 15. Effect of Ni on Growth of Aspergillus niger (507)

Control culture	0.77 g
Culture in the presence of $\frac{1}{15,000,000}$ Ni	0.74 g
Culture in the presence of $\frac{1}{5,000,000}$ Ni	0.78 g
Culture in the presence of $\frac{1}{1,500,000}$ Ni	0.74 g
Culture in the presence of $\frac{1}{500,000}$ Ni	0.826 g
Culture in the presence of $\frac{1}{150,000}$ Ni	0.837 g
Culture in the presence of $\frac{1}{50,000}$ Ni	0.860 g

Table 16. Effect of Ni on Growth of Aspergillus niger (507)

Control culture	0.445 g
Culture in the presence of $\frac{1}{500,000}$ Ni	0.457 g
Culture in the presence of $\frac{1}{25,000}$ Ni	0.580 g
Culture in the presence of $\frac{1}{15,000}$ Ni	0.670 g
Culture in the presence of $\frac{1}{10,000}$ Ni	0.607 g
Culture in the presence of $\frac{1}{7,500}$ Ni	0.40 g
Culture in the presence of $\frac{1}{3,000}$ Ni	myceliums were formed only at a few points

Coefficient of utility (for the optimal concentration): 1.50

Another study to determine the degree to which the plant fixes Ni is summarized in Table 17. The plant was found to fix Ni, but not all at its disposal. While the absolute quantity of Ni fixed increased with the quantity introduced, the ratio between the amount of Ni fixed and the amount introduced into the medium decreased.

Table 17. Fixation of Ni by Aspergillus niger (507)

Ni Introduced in 100 cm^3 of Milieu	Dilution	Dry Weight of Myceliums	Ni Fixed	Proportion of Ni fixed per 100 g of dry matter	Proportion of Ni fixed per 100 g Ni introduced
0.0002 g	$\frac{1}{500,000}$	0.705 g	0.00008 g	0.01	40
0.002 g	$\frac{1}{50,000}$	0.84 g	0.00062 g	0.073	31
0.004 g	$\frac{1}{25,000}$	0.986 g	0.00081 g	0.08	26.2
0.007 g	$\frac{1}{14,285}$	1.05 g	0.0013 g	0.12	18.5
0.010 g	$\frac{1}{10,000}$	0.986 g	0.0015 g	0.15	15

C. Batrachians and Reptiles

In 1939, Caujolle (111) reported that when comparing the relative toxicities of equimolar solutions of nickel and cobalt chloride it was found that:

a) Tadpoles of frogs died much more quickly in 0.001 M $NiCl_2$ solutions.

b) At the end of an equal time in which young grass snakes of similar weight were put into tanks containing 0.001, 0.0001, and 0.00001 M solutions, the percentage of dead reptiles was higher in the $NiCl_2$ solutions.

D. Mice

1. In 1953, Kincaid et al. (360) investigated whether $Ni(CO)_4$ was cumulative under conditions of repeated exposure over periods of a few weeks. For 48 days, five albino mice received 10 exposures of 30-minute duration each. The experiment is summarized in Table 18. The observations were:

a) The sixth and seventh exposures were equal to the LD_{50} for mice without any previous exposure and the tenth exposure was almost three times that value. No deaths occurred however, until after the tenth exposure.

b) The total accumulated exposure was equivalent to 0.76 mg/liter for 30 minutes (ca. 12 times the LD_{50} for mice without previous exposure).

Table 18

Multiple Exposures of Mice to Nickel Carbonyl* (360)

Exposure	Dose, Mg. per Liter	Time Between Exposure, Days	Total Time, Days
1	0.016	..	..
2	0.022	7	7
3	0.028	5	12
4	0.038	2	14
5	0.055	2	16
6	0.071	3	19
7	0.098	4	23
8	0.118	4	27
9	0.17	3	30
10	0.19	18	48

* All exposures were for 30 minutes. Five mice were used, and all survived until after the 10th exposure when two died.

The authors concluded that they had confirmed and extended the preliminary findings by Garland (reference in original paper) who found that:

a) $Ni(CO)_4$ was not cumulative

b) A tolerance was built up by giving small initial doses. (See also page 31, this Section, D2, and page 47, this Section, G.

2. In 1955, Hueper (284) extended his initial experimental studies of Ni carcinogenesis (282 and 283) in order to eliminate special strain-specific and species-specific influences.

a) Mice (25, strain C57BL male, 6 weeks old) were injected i.v. (tail vein) with 0.05 cc of an 0.005% Ni powder suspension in 2.5% gelatin solution. A second injection was given two weeks after the first one. The survival periods are shown in Table 19. Four mice died immediately after the second injection. Except for circulatory disturbances, there were no adverse, gross, or histologic observations.

Table 19

Survival Periods of Mice After Intravenous Injections of Nickel (284)

Months	0–1	5–15	13–14	15–16
Deaths	4	2	13	6

b) Mice (50, C57BL, 6 weeks old) were injected i.m. (right thigh muscle) with 0.02 cc of an 0.05% Ni powder suspension in a 2.5% gelatin solution. No tumors developed at the injection site. A few mice showed hyaline lesions in the spleen and liver. Mortalities during the experiment were: nine during first nine months; 15 during next three months; and 26 died or were sacrificed in the 13th to 18th month.

c) Mice (50, C57BL, male, 6 weeks old) were injected intrapleurally with 0.02 cc of an 0.06% Ni powder suspension in a 2.5% gelatin-saline solution. The survival periods are shown in

Table 20. Some of the mice had enlarged spleens, kidneys and livers with marked hyaline lesions. There were no tumors.

Table 20.

Survival Periods of Mice Intrapleurally Injected with Nickel (284)

Months	0-6	7-12	13-18	19-24
Deaths	8	5	33	4

The author concluded that the carcinogenic action of Ni was to a certain extent species-specific, since mice injected i.v., i.p., or i.m., did not develop cancers while rats (two strains) and rabbits developed tumors (see Biol., Section IV, page 72 and page 88).

3. In 1969 Weber and Reid (846) studied the influence of toxic levels of Ni on feed utilization, growth and reproduction in mice. Webster strain Swiss mice were used in both experiments in this study.

First experiment: Two levels of nickel (as the acetate salt); 1100 (157 mg/kg) and 1600 ppm (228.5 mg/kg) Ni were added to a basal diet and fed for four weeks to 12 mice (6 male and 6 female) per level. A third group of 12 animals received the unsupplemented diet. The effect of the ingested Ni on growth and feed consumption is summarized in Table 21.

Table 21 .

Effect of Nickel Acetate on Growth, Feed Consumption and Nickel Ingested (846)

Ni added, ppm	4-wk. wt./gm.		Feed consumed, gm./wk.		Ni ingested/ mouse, gm./wk.	
	Males	Females	Males	Females	Males	Females
0	24.2[a]	20.9[a]	34.8	28.7	T[c]	T
1100	23.2[a]	19.9[b]	32.1	26.5	35	29
1600	18.4[b]	17.5[b]	26.1	26.6	42	43

[a], [b] Means within sex differ significantly ($P<.05$).
[c] Trace.

The results were:

a) A significant reduction in growth when diets high in Ni were fed.

b) The feed consumption of males decreased with increased dietary Ni levels, while that of the females appeared to be relatively unaffected.

Second Experiment: Four pairs of weanling mice from the three previous dietary treatments (0, 1100 and 1600 ppm supplementary Ni), were weaned, matured and bred while kept on these same diets. Table 22 summarizes the adult body weights and the number of pups born and weaned.

Table 22

Effect of Nickel on Number of Pups Born and Weaned (846)

Ni added ppm	Adult body wt., gm.		Av. no. pups born	Av. no. pups weaned
	Males	Females		
0	33.2	33.8	10	7[a]
1100	31.5	32.8	9	7[a]
1600	31.9	31.9	8	2[b]

[a, b] Means with different superscript letters differ significantly ($P < .05$).

The results showed:

a) Body weights of adult mice were not affected by high Ni levels.

b) The average number of pups born and weaned decreased significantly ($P < 0.05$) at the higher (1600 ppm) Ni level as compared to the lower level (1100 ppm) and the controls.

E. Rats

1. In 1950, Phatak and Patwardhan (591) tested the effect of nickel (Ni) on rats after continuous ingestion for long periods. The Ni was administered in three forms: Ni catalyst, 19.7% Ni content, suspended in vegetable oil and supported in kieselguhr; Ni soaps of mixed acids of refined arachis oil, 10.2% Ni content; and nickel carbonate. The doses of the Ni test materials were fixed at three levels: 100 mg, 50 mg, and 25 mg, Ni per 100 g basal diet.

a) **Experiment with nickel carbonate:** Albino rats (four weeks old) were divided into four groups of eight each (4 male and 4 female). Each of the three diets was fed ad lib to one each of the groups for eight weeks. The fourth group served as control. The growth rates are summarized in Table 23.

Table 23.

Growth of Rats on Nickel Carbonate-Containing Diets (591)

Group & Ni content per 100 gm. diet	Average weights of eight rats in gm., Weeks								
	0	1	2	3	4	5	6	7	8
I — 100 mg.	43·0	58	66·7	76	85	92	86	109	115
II — 50 mg.	44·7	64	79·0	89	96	106	111	127	133
III — 25 mg.	43·0	65	79·8	92	99	109	113	129	135
Control	44·0	68	83·0	95	107	116	121	137	147

b) **Experiment with Ni Soaps and Catalyst:** Similar groups of eight rats each as in the previous experiment were treated in the same way. The nickel soap and catalyst respectively were incorporated into the basal diet at the same three levels described. A fresh control group was kept. The growth rates are summarized in Table 24.

Table 24 .

Growth of Rats on Nickel Soap and Catalyst (591)

Group & Ni content per 100 gm. diet	Average weight per week in gm., Weeks								
	0	1	2	3	4	5	6	7	8
Nickel Soaps									
I — 100 mg.	40·6	59·8	63·5	78·6	86·5	96·5	101·0	109·6	112·9
II — 50 mg.	38·0	56·1	62·7	70·8	81·5	86·7	105·6	113·3	120·6
III — 25 mg.	38·1	59·7	62·6	73·7	85·1	102·0	107.0	112·8	123·2
Nickel Catalysts									
IV — 100 mg.	35·1	54·2	59·1	67·2	78·8	97·8	101·7	108·5	113·2
V — 50 mg.	34·1	55·8	60·1	73·5	85·1	103.0	106·0	118·6	125·2
VI — 25 mg.	36·0	59·4	67·8	78·8	93·7	107·0	116·2	125·4	128·5
Controls for groups I to VI	41·9	66·5	71·2	86·1	98·0	112·0	117·0	126·7	132·6

c) Reproduction Experiment: After the eight-week feeding period the males and females of each of the feeding groups were paired and mated. The same diets as in experiments (a) and (b) were continued throughout gestation and lactation — a period of three to four months. The amount of Ni in the whole body was determined for two animals from each liter. The results are summarized in Table 25.

Table 25.

Nickel in the Bodies of New-Born Rats (591)

Group No. & mg. of Ni/100 gm. diet	No. of young ones in litter	Weight of young ones, gm.	Nickel, mg./100 gm. body weight
$NiCO_3$			
I — 100	3	4·5	2·21
		4·3	3·00
	5	4·2	2·19
		4·3	2·78
II — 50	9	4·7	1·70
		4·7	1·37
	6	4·0	1·24
		3·7	1·62
III — 25	5	4·1	nil
		3·9	nil
	6	4·8	nil
		4·6	nil
Control	8	3·1	nil
		3·9	nil
	10	4·0	nil
		4·3	nil
Nickel Soap			
I — 100	6	3·7	nil
		3·6	nil
	4	4·0	0·12
		4·1	0·18
II — 50	5	4·4	nil
		4·5	nil
	7	3·9	nil
		3·9	nil
III — 25	5	4·7	nil
		4·0	nil
	5	4·3	nil
		4·4	nil
Nickel Catalyst			
IV — 100	5	4·6	0·44
		4·6	0·33
	7	4·2	0·12
		4·3	0·15
V — 50	8	4·2	nil
		4·2	nil
	8	4·5	nil
		4·5	nil
VI — 25	7	3·9	nil
		4·0	nil
	8	4·3	nil
		4·3	nil
Control	9	4·9	nil
		5·0	nil

The authors concluded that:

a) There were no significant differences in the growth rate (eight weeks) of rats on Ni-containing diets as compared with the controls.

b) There were no differences among the respective groups in reproduction performance.

c) In general, the overall condition of rats surviving after three to four months of Ni diets was similar to that of the controls.

d) The highest Ni content was found in one-day old infants of mothers fed 100 mg per 100 g ration of nickel carbonate. Ni was found in all the one-day olds of mothers on the highest intake of any of the three test materials while no Ni could be detected in those infants from mothers on the lowest intake of these materials (25 mg per 100 g ration).

2. In 1953 Kincaid et al. (360) exposed Wistar strain albino rats to $Ni(CO)_4$ in an experiment which was similar to the one with mice described on page 30 (this Section D1) with similar results. The experiment is summarized in Table 26.

Table 26.

Multiple Exposures of Rats to Nickel Carbonyl (360)

Exposure	Dose, Mg. per Liter	Time Between Exposure, Days	Total Time, Days
1	0.083	..	..
2	0.14	2	2
3	0.20	4	6
4	0.20	3	9
5	0.40	3	12
6	0.10	3	15
7	0.44	4	19
8	0.51	7	26
9	0.52	11	40
10	0.54	8	48

* All exposures were for 30 minutes. One rat out of the group of six died following the 9th exposure; all others survived.

The authors concluded from their observations that the deaths of the mice and rats took place when the time between exposures was two or more weeks, that the increased tolerance from repeated $Ni(CO)_4$ exposure was of relatively short duration.

These results were taken as confirmation and extension of Garland's findings, (See reference original paper and page 30, this Section D1.)

Another study with the same strain of rats was carried out to determine the effect on the blood of animals exposed to $Ni(CO)_4$. The experimental animals were subjected to exposures equal to or exceeding their LD_{50} (0.24 mg/liter for 30 minutes). The results of the hematologic studies (CO concentration, coagulation, prothrombin, platelets, blood counts, abnormal hemoglobin pigments) indicated that the only changes following exposure were a moderate hemoconcentration and a slight leucocytosis.

3. In 1955 Hueper (284) injected 25 three-month old Wistar rats (100 - 184 g) in the vena saphena with 0.5% Ni suspension in physiological saline. The dose was 0.5 cc/kg BW (0.1 - 0.18 cc/rat). Six injections were given at one-week intervals. The observation period extended over 28 months. No significant changes were found in comparing differential leukocyte counts before the first injection with two made during the last eight months following injection. The survival periods are shown in Table 27.

Table 27.

Survival Periods of Rats After Repeated Intravenous Injections of Nickel (284)

Months.....	0-3	4-6	7-9	10-12	13-18	19-24	25-28
Deaths.....	5	3	10	1	0	3	3
Tumors.....	0	0	7	0	0	0	0

4. In 1966 Chernen'kii and Smirnova (119) studied the effects in rats of p.o. administration of Ni (as the soluble salt, $NiCl_2$). Their interest was the result of what they considered conflicting reports of the oral toxicity of Ni, pointing out that on the one hand:

a) Plants growing in Ni-rich regions have been known to grow in abnormal shapes.

b) Animals in such regions accumulate Ni in their fur, skin and bones, with young sheep and cows frequently suffering

from eye diseases such as keratitis and keratoconjunctivitis (Cherkinskiy; Voynar; both sources referenced in original paper).

On the other hand, they noted that the amount of Ni/day which would be ingested by a person cooking in Ni utensils, 2 mg/kg/day, is not considered toxic by most investigators and that a dose of 100 µg/kg has not been found toxic in experimental animals (Leman, referenced in original paper).

A solution of $NiCl_2$, at doses of 0.06, 0.12 and 0.3 mg/kg (Ni equivalent) was administered by intubation to three groups of 10 white rats each for 13 days (10 controls received distilled water).

The observations included:

a) Appearance, behavior and weight.

b) Blood: number erythrocytes, and leukocytes in the peripheral blood at regular intervals, and the color index and blood catalase activity before and after.

The results were:

a) Animals appeared healthy and active with normal appetites.

b) The animals receiving 0.12 and 0.3 mg/kg showed a reduction in weight increase. This was most marked in the 0.3 mg/kg group in which it was 18% of the control value.

c) During the first 60 days, the number of erythrocytes in the experimental animals was somewhat smaller than the controls. No change was seen in leukocyte number.

d) There was a decrease in blood catalase activity in the experimental animals which was not dose related.

e) No gross or microscopic changes in rat organs examined (heart, lung, liver, spleen and kidney) were detected in contrast to Grushko's findings (reference in original paper).

The authors concluded that their experiments suggested that protracted p.o. administration of Ni may not be innocuous for animals.

5. In 1969 Itskova et al. (303) studied the effects of nickel salts given orally daily over a prolonged period. The author's interest in the oral toxicity of soluble nickel salts was due to the presence of "abnormal amounts" of nickel in a number of Russian water supply sources. The two main origins of Ni contamination cited were from the effluent of processing polymetallic ores and from nickel-rich regions.

Two experiments were carried out in which aqueous solutions of varying concentrations of two Ni salts ($NiCl_2 \cdot 6H_2O$ and $NiSO_4 \cdot 7H_2O$) were administered via stomach tube once daily (1 ml/100 g) to white rats (male and female, 150-170 g).

Experiment 1: Two experimental groups, 20 rats in each, were administered, respectively, 5 mg/kg and 20 mg/kg Ni (as $NiCl_2 \cdot 6H_2O$) for 40 days. There were 10 controls. No animals died. After 40 days, half the animals of each experimental group were given a dose equal to the LD_{50} (105 mg/kg for males and 129 mg/kg for females). Three experimental rats died, two from the group which had received 20 mg/kg. (Two controls also died.) The authors concluded from this data as well as from the lack of mortality among the animals receiving a total Ni dosage twice and eight times the LD_{50}, that Ni does not have cumulative properties (see also page 31, this section D2).

Experiment 2: In the course of seven months, 72 rats, divided into five groups (plus one control group) were administered the following daily Ni doses: 0.0005 mg/kg, 0.005 mg/kg, 0.05 mg/kg, 0.5 mg/kg and 5.0 mg/kg.

The results of these two experiments were:

a) The experimental animals did not increase in weight as much as the controls (see Figure 2). At 5 mg/kg, the difference was statistically significant ($P < 0.05$).

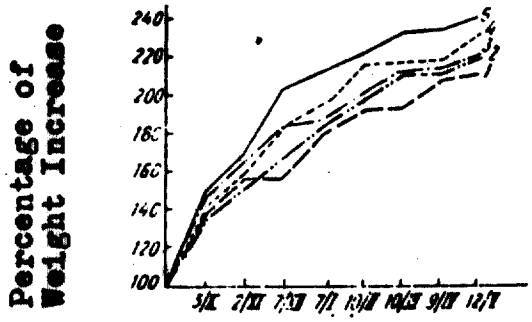

Figure 2. The Dynamics of the Weight of Animals During Daily Introduction Per Os of Chlorous Nickel in a Dose of 5 (1); 0.5 (2); 0.005 (3) and 0.0005 mg/kg (4) in Comparison with the Control (5).(303)

b) Examination of the organs and tissues showed noticeable changes in the mucuous membranes of the upper section of the small intestine with an intensified proliferation reaction of the villi of the epithelium and a round-cell infiltration of their stroma.

c) Oral administration of Ni had no effect on blood composition hemoglobin and maintenance of albumin and sulfhydryl groups in the serum. The authors suggested that the lack of effect on blood with oral as compared to parenteral administration of Ni might be owing to the excretion of 90% of Ni introduced per os unabsorbed.

6. In 1970 Hackett and Sunderman (243) investigated the ultrastructural reactions of the rat hepatocyte following injection of $Ni(CO)_4$. Two dosage levels were injected in the tail vein of Sprague-Dawley rats (Male, 120 - 150 g, number not stated); LD_{50}, 2.2 mg Ni/100 mg BW and LD_{100}, 6.6 mg Ni/100 g. Two or three rats were sacrificed at one time at nine intervals from 0 hour up to six days. The rats developed severe respiratory symptoms.

The symptoms observed from electron microscopic examination of liver sections were:

a) At the LD_{100} dosage level, alterations in the endoplasmic reticulum were seen as early as two hours and were present in nearly all the hepatocytes by 24 hours.

b) These changes were also noted at the LD_{50} dosage level but developed more slowly involving fewer hepatocytes.

c) In rats surviving the LD_{50} injection, the hepatic ultrastructure returned to normal by the sixth day.

d) The majority of the mitochondria, as well as other cytoplasmic organelles showed no pathologic alterations.

7. In 1971 Schroeder and Mitchener (672) studied the toxic effects of Ni on the reproduction of rats when given in doses tolerable for growth and survival. Five pair of Long-Evans BLV:(LE) strain rats born and bred in a trace-metal free environment were given 5 ppm Ni (as a soluble salt equivalent to 0.5 mg/kg/day) in drinking water continuously. The diet contained 0.31 ppm Ni (equivalent to Ca. 0.033 mg/kg/day). Each group was carried through three generations.

A summary of the breeding experiment is shown in Table 28. The deaths and abnormalities are summarized in Table 29.

The results showed:

a) In the first generation: 9.1% young deaths, one maternal death, and 30.6% runts.

b) In the second generation: 10.2% young deaths, and 5.1% runts.

c) In the third generation: 21.0% (17) young deaths and 6.2% (5) runts.

d) With each generation, the size of the litters decreased.

e) With two failures to breed, the number of rats was reduced.

f) Few males were born in the third generation.

Table 28.

Summary of Breeding Experiments in Rats Exposed to Nickel (672)

	No. of Litters	Pair Age at First Litter (Days)	Interval Between Litters (Days)	Average Litter Size	M-F Ratio
F_1 Generation					
Control	10	89	41	11.4	1.14
Nickel	11	101	42	11.0	1.20
F_2 Generation					
Control	10	87	40	11.3	1.10
Nickel	15	98	38	10.5	1.18
F_3 Generation					
Control	11	86	41	11.0	1.06
Nickel	10	92	30	8.1	0.44

The authors concluded that:

a) Ni was moderately toxic on a scale in which lead was the most toxic trace element.

b) Developing male rats *in utero* were more vulnerable to Ni than developing females.

c) Feeding an element for life is not as sensitive a method for detecting toxicity as this type of reproductive study because as this experiment showed, certain trace elements fed in doses which do not interfere with growth or survival are intolerable for normal reproduction.

Table 29.

Deaths and Abnormalities in Rats Bred While Exposed to Nickel (672)

	Control	Nickel
F_1 Generation		
Maternal Deaths	0	1
Dead Litters	0	0
Young Deaths	0	11*
Failures to Breed	0	0
Runts	0	37‡
No. of Rats	114	121
F_2 Generation		
Maternal Deaths	0	0
Dead Litters	0	0
Young Deaths	0	16‡
Failures to Breed	0	2
Runts	1	8
No. of Rats	113	157
F_3 Generation		
Maternal Deaths	0	0
Dead Litters	0	0
Young Deaths	1	17*
Failures to Breed	0	0
Runts	0	5†
No. of Rats	121	81
Total No. of Rats	348	359

* Differs from Controls by χ^2 Analysis; $P < 0.005$.
† $P < 0.0001$.
‡ $P < 0.025$.

F. Chicks

1. In 1968 Weber and Reid (847) evaluated the effects of high levels of Ni on the growth of chicks. Two studies were conducted with 4-week old Hubbard broiler chicks. In both experiments, three groups of eight chicks each (4 male and 4 female) were fed each of the experimental diets.

Experiment 1: Nickel sulfate or acetate was added to the basal diet to supply the following amounts of Ni: 0, 100, 300, 500, 700, 900, 1100 and 1300 ppm (equivalent to 12.5, 37.5, 62.5, 87.5, 112.5 and 132.5 mg/kg/day). The diets were fed ad libitum.

Experiment 2: To evaluate the separate effects of Ni on feed consumption and protein utilization, 1100 ppm level of Ni (as sulfate or acetate) was fed and the basal diet was pair-fed with these diets. The basal diet was fed ad libitum to a separate group.

The results of these experiments are summarized in Tables 30-34.

Table 30.

Effect of Dietary Nickel Sulfate on Body Weight, Feed Utilization and Levels of Nickel Ingested in Chicks (847)

Nickel added as nickel sulfate	Body wt, 4 weeks	Feed conversion	Calculated nickel ingested to gain	Calculated nickel consumed per bird
ppm	g		mg/g	mg
0	565 a [1]	1.78	T [2]	T
100	534 a	1.73	151	87
300	568 a	1.68	453	269
500	467 ab	1.69	687	406
700	376 b	1.97	794	412
900	247 c	2.11	837	396
1100	180 c	2.38	889	373
1300	179 c	2.82	1,347	478

[1] Means having different superscripts are statistically different at the 0.05 level of probability.
[2] T = trace.

Table 31

Effects of Dietary Nickel Acetate on Body Weights, Feed Utilization and Levels of Nickel Ingested in Chicks (847)

Nickel added as nickel acetate	Body wt, 4 weeks	Feed conversion	Calculated nickel ingested to gain	Calculated nickel consumed per bird
ppm	*g*		*mg/g*	*mg*
0	565 [a 1]	1.78	T [2]	T
100	514 [a]	1.79	152	85
300	559 [a]	1.66	429	259
500	484 [ab]	1.71	656	383
700	390 [b]	1.79	795	444
900	259 [c]	2.13	870	409
1100	256 [c]	2.04	1009	483
1300	173 [c]	2.54	1155	454

[1] Means having different superscripts are statistically different at the 0.05 level of probability.
[2] T = trace.

a) As can be seen in Tables 30 and 31, the form of Ni fed had no significant effect on their growth. When fed as either the acetate or sulfate, Ni caused a progressive growth depression.

b) The authors concluded that the amount of Ni ingested controlled the level of feed consumption.

c) As the level of Ni increased (from nickel sulfate), the amount of nitrogen retained decreased (see Table 32). Protein ratios also decreased with higher levels of nickel sulfate.

Table 32

Effect of Nickel Sulfate on the Metabolism of Some Dietary Nutrients (847)

Nickel added	Gross energy retention	Metabolizable energy	Fat retention	Nitrogen retained	Protein efficiency ratio
ppm	%	*kcal/g feed*	%	%	
0	64.83	2.72	69.46	41.16	2.44
100	63.96	2.68	67.06	41.64	2.51
300	65.66	2.76	69.58	41.58	2.59
500	62.29	2.61	64.80	33.00	2.57
700	58.37	2.37	68.33	19.57	2.21
900	58.03	2.44	72.50	16.17	2.06
1100	56.06	2.35	75.75	12.50	1.83
1300	52.05	2.19	71.79	11.27	1.54

d) When nickel acetate was fed, the reduction in nitrogen retention occurred at the 900 ppm level as compared with 300 ppm for nickel sulfate. (See Table 33.) A similar difference was noted with respect to the levels at which protein ratios decreased.

Table 33

Effect of Nickel Acetate on the Metabolism of Some Dietary Nutrients (847)

Nickel added	Gross energy retention	Metabolizable energy	Fat retention	Nitrogen retained	Protein efficiency ratio
ppm	%	kcal/g feed	%	%	
0	64.83	2.72	69.46	41.16	2.44
100	63.43	2.66	69.78	33.96	2.43
300	63.89	2.68	64.97	36.99	2.62
500	65.80	2.76	71.79	36.67	2.54
700	64.56	2.71	72.49	36.11	2.43
900	62.56	2.63	79.06	28.28	2.04
1100	58.33	2.45	73.03	20.34	2.06
1300	58.48	2.46	75.26	15.82	1.71

e) The results of the second experiment (see Table 34) along with those of the previous experiment suggested to the authors that Ni in addition to having an effect on feed intake, was detrimental to nitrogen retention.

Table 34 .

Effect of Dietary Nickel on Pair-Fed Chicks (847)

Dietary treatment	Avg body wt 4 weeks	Feed consumed per bird	Feed conversion	Nitrogen retention
	g	g		%
1. Basal diet ad libitum	570 a,1	905	1.74	54.4
2. 1100 ppm Ni as nickel acetate ad libitum	304 b	538	2.12	44.9
3. Basal diet pair-fed with treatment 2	292 b	501	2.07	58.1
4. 1100 ppm Ni as nickel sulfate ad libitum	262 b	490	2.31	46.5
5. Basal diet pair-fed with treatment 4	259 b	451	2.16	63.4

[1] Means having different superscripts are statistically different at the 0.05 level of probability.

2. In 1970 Nielsen and Sauberlich (537) investigated whether Ni performs a physiological role for the chick. Day-old White Rock chicks were put on a low Ni diet for three weeks (< 0.08 ppm Ni) while controls were fed a diet supplemented with 5 ppm $NiCl_2 \cdot 6H_2O$. Two experiments were carried out:

Experiment 1: A total of 10 three-week old chicks were given 20 $\mu Ci\ ^{63}Ni$ (as $^{63}NiCl_2$) by gavage (4 µg Ni).

Experiment 2: A total of 18 three-week old chicks were given 25 $\mu Ci\ ^{63}Ni$ by gavage (4 µg Ni).

It was observed that:

a) The gross appearance of the checks was affected by the amount of Ni in the diet in both experiments.

b) The two most notable effects were: leg color and leg development (slightly thickened legs with somewhat swollen hock joints).

c) There was no significant effect of dietary Ni on body weight (see Table 35).

Table 35

Body Weights and Tibia Length: With Ratios of Chicks Fed Different Levels of Nickel (537)

Experiment[a]	Dietary nickel ppm	Body[b] weights (g)	Length:width ratio of tibia
1	< 0.08[c]	130	--
1	5.00	128	--
2	< 0.08[c]	121	17.62[d]
2	5.00	109	18.38[d]

[a]Mean of 5 chicks in experiment 1; 10 chicks in experiment 2.
[b]Body weights at 3 weeks of age.
[c]Nickel content by analysis of diet with no supplemental nickel.
[d]Significant difference at the 0.05 level.

The authors concluded that since the observed symptoms in the low dietary Ni chicks were not observed in the controls (Ni supplemented diet), Ni has a physiological role in the chick (see also page 107, Biochemistry Data II D).

3. In 1972 Sunderman et al. (742) investigated the effects of nickel deficiency in chicks. Newly hatched chicks (24) were divided into two groups: 12 were fed a low Ni diet (44 ppb Ni) and 12 were fed the same diet supplemented with $NiCl_2$ (3.4 ppm Ni). The observations after 30 days were:

a) No significant differences were found between the two groups with respect to: body weights; appearance of legs on physical and X-ray examination (did not confirm Nielsen and Sauberlich (537), page 46 , this Section F2); hematological parameters; concentration of serum cholesterol (did not confirm Schroeder's (670) findings with rats, page 136, Biochemical Data IV C5); histological appearance of organs and tissues by light microscopy.

b) An abnormality in the hepatocytes of three out of four Ni-deprived chicks, dilatation of the perimitochondrial rough endoplasmic reticulum, was not detected in any of the controls.

The authors concluded that they had been unable to produce evidence of a Ni-deficiency syndrome.

G. Ducks

In 1968 Grandy et al. (227) conducted a 30-day toxicity test with pen-reared mallard drakes (18 months old) to determine the relative toxicity of various types of metal shot. Only the Ni shot is discussed here. Three groups of five ducks each, except controls, were dosed with eight number 6 shot. The animals were sacrificed 30 days after dosage. The results are summarized in Tables 36 and 37 , which follow.

Table 36

Mortality and Weight Losses Among Mallard Drakes, During 30 Days After Force-Feeding Ni Shot* (227)

Shot Type	Mortality Among Three 5-Bird Replicates			Percentage Mortality	Post-Dosage Days to Death		Percentages of Weight Loss			
							Dead Birds		Survivors	
					Avg.	Range	Avg.	SD	Ave.	SD
92% nickel, 5.5% silicon, 1.7% iron, 0.8% trace elements	0	0	0	0	--	--	--	--	20‡	11.85

*15 Birds, each Bird given 8 Shot.
‡ note p. 485

Table 37.

Concentration of Iron (ppm Wet Weight) in Livers of Ducks Treated with Ni Shot (227)

Nickel	Control
1,703	954
1,976	950
1,472	1,153
3,050	2,921
2,054	1,210

In summary,

a) None of the Ni shot dosed birds died during the study.

b) The weight loss averaged 20% of BW, and was significantly greater than controls.

H. Rabbits

1. In 1955 Hueper (284) injected i.v. 10 albino rabbits (2,000 - 3,000 g wt.) with a 1% powdered Ni suspension (0.5ccc/kg BW) in a 25% gelatin solution, at weekly intervals for six weeks. Five controls were injected i.v. with similar amounts of the 25% gelatin solution. The injections were poorly tolerated. Several animals gained weight during the injections while others lost several hundred grams. Two rabbits died in the fourth and twelfth month after the start of the experiment with paresis of the hind legs. The controls remained healthy 40 months after start of the experiment. The survival periods are shown in Table 38.

Table 38 .

Survival Periods of Rabbits After Repeated Intravenous Nickel Injections (284)

Months.....	0-12	13-18	19-24	25-32	33-36	37-44
Deaths.....	4	1	1	3	1	Test series

2. In 1958 Kadota and Kurita (317) studied the hyperglycemic effect of nickelous chloride ($NiCl_2$). Doses of 10 to 15 mg/kg $NiCl_2$ were given i.v. to 22 adult rabbits (rabbits receiving 20 mg/kg BW died immediately following injection).

The changes in blood sugar are shown in Table 39 and Figure 3 .

Table 39.

Changes in Blood Sugar After Intravenous Injection of 0.5% Nickelous Chloride Aqueous Solution (317)

Rabbit	Body wt (gm)	Injected dose (mg/kg)	Blood sugar; mg. 100 ml. of Blood						
			Before injection	Hrs. after injection					
				1	2	3	4	10	24	48
94	2,120	10	79	217	191		110		76	82
95	2,100	10	71	79	98		79		98	95
101	2,180	10	105	163	147		88		123	
102	1,980	10	107	217		307		905	110	
103	2,320	10	77	95	95		89		72	75
104	2,000	10	93	172	132		86		109	112
105	2,080	10	89	111	81		89		79	
106	3,220	10	77	81	93		82		81	
107	1,960	10	96	125	93		115		100	
108	2,200	10	109	158	113		107		100	
109	2,000	10	95	165	127		101		127	
96	2,100	15	116	215	185	141			127	125
125	1,980	15	127	211	273		210		139	
126	2,000	15	79	168	163		121		91	95
127	2,100	15	86	153						
129	2,000	15	76	135	107				80	
130	2,000	15	90	152	137		183			
131	2,100	15	111	236	167		220			
128	2,250	20	77	163						
155	2,000	20	81	153		237			93	
156	2,000	20	73	117		150			85	
157	2,000	20	91	121	156		230		80	
Second injection after 18 hrs.										
102	2,020	10	123	186	167		121		116	
103	2,320	10	88	97	107		74		75	

The observations were:

a) With 10 mg/kg doses, 7 out of 11 animals showed transitory hyperglycemia after one to four hours.

b) With 15 to 20 mg/kg doses, all animals showed from 150 to 300 mg percent hyperglycemia, returning to normal after 24 hours.

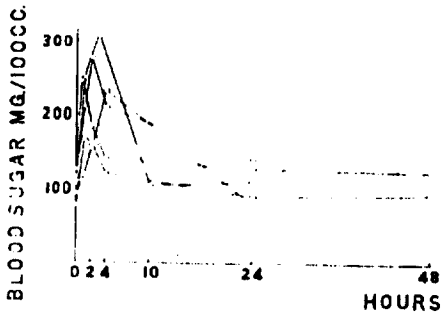

Figure 3. Changes in Blood Sugar Level in Rabbits After Intravenous Administration of 15 to 20 mg' per Kilogram of Nickelous Chloride (317)

c) A second injection of 10 mg/kg caused a new transitory hyperglycemia.

d) When Alloxan diabetic rabbits were administered 200 mg/kg $NiCl_2$, hyperglycemia was augmented (see Table 40.

Table 40.

Changes in Blood Sugar After Intravenous Injection of Nickelous Chloride in Alloxan Diabetic Rabbits (317)

Rabbits	Alloxan doses (mg./kg.)	Duration of hyperglycemia (days)	Body wt. (gm.)	Injected NiCl doses (mg./kg.)	Blood sugar, mg. 100 ml. of blood						
					Before injection	Hrs. after injection					
						1	2	3	4	21	48
154	200	30	2,260	15	151	171	168		160	155	157
158	200	23	1,900	15	152	212	207	222		251	311
158	200	30	1,600	15	191	270		260		316	240
								(after 1 week)			
159	200	15	2,000	20	164	286					
160	200	21	1,300	30	186	151	176		150		

e) In the islet cells in the pancreas of rabbits receiving $NiCl_2$, there was destruction of alpha cells and to a lesser degree beta cell damage with degranulation. After 24 hours, the cellular damage was more severe.

3. In 1965 Tardivel et al. (767) carried out two experiments in which Ni was administered to rabbits daily for nine months, at which time they were sacrificed.

Experiment 1: Ten animals were administered p.o. 5 to 20 mg/kg pulverized Ni daily. The animals appeared to be in "perfect physical condition" at the end of the nine month experimental period when they were sacrificed.

Experiment 2: Ten animals were administered p.o. 100 to 500 mg/kg pure Ni powder daily. The authors noted that contrary to results obtained in a previous experiment with guinea pigs, the rabbits subjected to high doses survived with good maintenance of general health.

The experimental results for the first experiment showed, however, that despite the lack of clinical evidence of intoxication, 90% of the animals showed physiological changes. The authors noted that the hematological picture was similar to that previously found with guinea pigs, a leucocytosis with lymphocytosis, varying from 9,000 to 18,000 leucocytes with an average of 60 to 80% lymphocytes.

The animals in the second experiment also showed a leucocytosis of between 15,000 and 20,000 per cubic mm.

The red blood cells were quantitatively and qualitatively normal. An electrophoretic study of the blood serum showed changes affecting the globulin distribution; the $\alpha 1$ globulins were statistically increased while the $\alpha 2$ and γ globulins were decreased from 50 to 75% of normal.

The authors concluded that the hematological and electrophoretic changes consistently found in all the experimental animals were directly related to the Ni administered.

I. Cats

In 1953 Kincaid et al. (360) exposed a single cat to $Ni(CO)_4$ in an experiment similar to the ones with mice, page 30, (this Section, D1) and rats, page 36 (this section E2). After the first exposure the cat became noticeably ill, but no symptoms were observed after the other exposures (the sixth exposure was equal

to the LD_{50} for cats without previous exposure). Again, the results were similar to those with mice and rats (see page 30, this Section D1 and page 36, this section E2) namely that exposure to $Ni(CO)_4$ produced a tolerance to it, a further confirmation as with mice and rats of Garland's preliminary findings (see original paper for reference). This experiment is summarized in Table 41.

Table 41.

Multiple Exposures of a Cat to Nickel Carbonyl* (360)

Exposure	Dose, Mg. per Liter	Total Time After First Exposure, Days
1	0.50	..
2	0.61	37
3	1.60	67
4	1.68	81
5	1.24	111
6	1.05	125

* All exposures were for 30 minutes.

J. Calves

In 1970 O'Dell et al. (550) studied the effects of high Ni levels fed to calves with respect to growth, feed utilization and tissue aberrations. At the end of a one-week preliminary period on an experimental basal diet, 20 Holstein and three Brown Swiss male calves (13 weeks old) each received one of four diets for eight weeks, consisting of the basal diet supplemented with Ni (as $NiCO_3$) as follows: 0, 62.5, 250 and 1,000 ppm (equivalent to 1, 4 and 15.5 mg/kg/day). Twelve of the animals (three per treatment) were killed for histological study at the end of the eight-week treatment period. The remaining animals were returned to the basal diet for a six-week recovery period.

The results were:

a) The 250 ppm diet reduced feed consumption and weight gains by 13% and 11% respectively (significant at the 20% probability level).

b) All animals on 1000 ppm Ni diet drastically reduced feed intake ($P < 0.001$), and all lost weight.

c) The animals on the 1000 ppm Ni diet developed an immediate aversion to it and did not adapt to it.

d) Growth data (see Table 42) are plotted against Ni levels in Figure 4 . By interpolation, it can be seen that a reduction in growth rate significant at the 5% level would occur at 300 ppm Ni and a zero gain at 900 ppm Ni.

Table 42.

Average Weight, Daily Feed Consumption and Daily Live Weight Gains of Young Dairy Bulls Fed Nickel-Supplemented Diets for 8 Weeks and During a 6-Week Recovery Period When the Basal Diet was Fed (550)

	Level of nickel supplementation, ppm				SE[1]
	0	62.5	250	1000	
	kg				
Treatment period [2]					
Initial weight	113	110	114	111	
Feed consumption	5.58[a,3]	5.34[a]	4.87[a]	1.41[b]	0.34
Rate of gain	1.33[a]	1.35[a]	1.13[a]	−0.16[b]	0.10
Posttreatment period [4]					
Initial weight	186	155	175	99	
Feed consumption	7.81[c,5]	6.50[cd]	6.30[cd]	4.67[d]	0.55
Feed intake/100 kg avg wt	3.41	3.17	2.94	3.29	
Rate of gain	1.47[c]	1.37[c]	1.39[c]	1.51[c]	0.24

[1] Standard error of a treatment mean calculated from pooled error mean square in analysis of variance.
[2] Six animals per treatment (five on 62.5 ppm).
[3] Within each measurement, those values not followed by the same letter are significantly different at the 0.1% probability level.
[4] Three animals per treatment (two on 62.5 ppm).
[5] Within each measurement those values not followed by the same letter are significantly different at the 5% probability level.

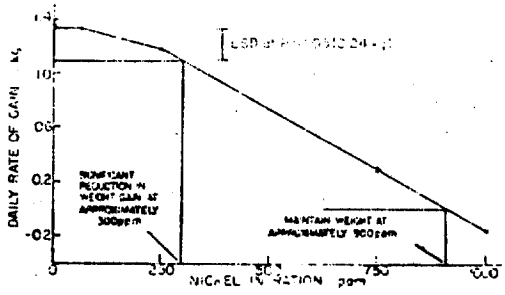

Figure 4. Average Daily Rate of Gain by Male Calves Fed Nickel at Levels of 0, 62.5, 250 or 1000 ppm of Total Ration and Estimation of Nickel Level that Would Result in Statistically Significant Reductions in Rate of Gain or Maintenance of Initial Weight (no gain). SE of a Treatment Mean was ± 0.10 kg with Six Animals per Treatment (5 on 62.5 ppm). (550)

e) Histopathologically the only tissue affected was kidney (see Table 43). The kidney damage increased in severity as the level of Ni increased culminating in pyelonephritis.

Table 43 .

Effect of Nickelous Carbonate on Histopathological Changes in Selected Tissues(550)

Nickel suppl. in ppm	Animal no.	Tissue					
		Rumen	Abomasum	Duodenum	Liver	Kidney	Testis
0	1	N *	N	2	N	5	N
	2	1	1	N	3	6,7	N
	3	N	2	N	4	5	N
62.5	1	N	N	N	N	5	N
	2	N	N	8	N	6,9	N
	3	N	N	N	N	6,7	N
250	1	N	N	N	N	5,8,9	N
	2	N	N	N	N	6,10	N
	3	N	N	N	N	5	N
1000	1	N	N	N	N	5,6	N
	2	N	N	N	11	12	N
	3	1	1	N	3	.	N

* Explanation of code: N, Normal; 1, cellular infiltration; 2, gastroenteritis; 3, proliferation of bile duct epithelium; 4, focal necrosis; abscesses; 5, glomerulo interstitial nephritis; 6, dilation of collecting tubules; 7, cellular infiltration of interstitial and glomeruli tissues; 8, lymphocyte infiltration with congestion; 9, congestion of medulla; 10; hyaline cast in collecting tubules; 11, extramedullary hematopoiesis; 12; pyelonephritis.

The authors concluded that reduced feed intake and rate of gain may be a physiological response to Ni intake.

K. Monkeys

In 1950 Phatak and Patwardhan (591) fed adult monkeys (Macacus sinicus) nickel-containing diets for 24 weeks. Ni in the form of nickel carbonate, nickel soaps of mixed fatty acids of groundnut oil and nickel catalyst were mixed with a basal diet to give 100, 50 and 25 mg Ni per 100 g mixture. The monkeys received 100 g food daily (see Table 44). Maintenance of weight, general behavior and other toxic manifestations were used as criteria for Ni toxicity.

Table 44.

Distribution of Monkeys on Nickel-Containing Diets (591)

Level of Ni, mg./100 gm. food	Diets containing		
	Nickel carbonate	Nickel soap	Nickel catalyst
	No. of animals		
100	2	...	...
50	2	2	2
25	2	2	...
Nil	Two animals served as controls		

The results are summarized in Table 45.

Table 45.

Body Weights and Blood Findings in Monkeys Kept on Nickel-Containing Diets (591)

Group No. & mg. of Ni/100 gm. diet	Serial No. of monkeys	Weight in lb.		Blood findings at 6 months		
		Initial	At 24 weeks	R.B.C. mill/c.m.m.	Haemoglobin gm./100 c.c.	W.B.C. per c.m.m.
Nickel Carbonate						
I — 100	1	6·00	6·50	6·50	14·4	19,200
	2	6·25	7·25	6·93	12·7	16,800
II — 50	3	7·25	8·75	6·17	14·4	...
	4	6·50	7·25	6·90	16·6	13,200
III — 25	5	5·25	6·50	6·92	13·9	13,200
	6	5·25	6·50	6·25	13·6	14,800
Nickel Soap						
II — 50	7	6·00	6·00	6·53	16·9	18,200
	8	5·75	Died after 22 weeks (wt. 5·5)	...	...	...
III — 25	9	4·50	4·00	7·06	14·4	17,000
	10	5·25	5·25	6·51	14·8	20,400
Nickel Catalyst						
II — 50	11	4·50	5·25	6·68	13·6	15,650
	12	5·75	6·50	6·27	12·7	17,600
Control	C1	4·50	4·50	7·50	13·9	16,350
	C2	4·25	5·00	...	...	...

The authors concluded that:

a) At the levels of Ni intake tested over a 6-month period, the animals maintained their weight and were in perfect health at the conclusion of the experiment.

b) The hemoglobin, R.B.C. and W.B.C. blood counts were normal. (For a similar study with rats, see Section E1, page 33 .)

L. Humans

1. In 1934 Brandes (087) reported the case of a chemist (male, 49 years old) who died on the seventh day after brief exposure to $Ni(CO)_4$, when pouring it from one container to another. Histologic examination showed the most marked changes in the lung and brain such as edema, hyperemia, multiple hemorrhages and changes in the cells lining the alveoli in the lungs and multiple small hemorrhages particularly numerous in the white substance of the brain. Analysis for Ni in 3 g each of lung and brain tissue (dimethylglyoxime test, sensitive to 0.001 mg Ni) gave a strong reaction in lung and a weaker reaction in brain. Post-mortem blood examination gave a negative CO test. The author concluded that the clinical and pathological

changes were due to Ni and corresponded closely to previously reported cases of Ni poisoning (see original paper for references).

2. In 1947 Van Arsdell (813) described the toxic nature of various metal compounds used in the plating industry. The report described the effects of Ni and its salts as follows:

a) Some persons were susceptible to the inhalation of Ni dusts with symptoms of throat irritation, weakness, fever, headache, nausea, muscle and joint pains.

b) More widespread reaction was caused by the soluble Ni salts, chloride, nitrate and sulfate, which resulted in a dermatitis.

c) Ingestion of these Ni salts initially caused vomiting.

3. In 1960 Herring et al. (268) reviewed the toxicity of Ni to humans as follows:

a) Ni is a probable cause of carcinoma of the respiratory tract. The responsible agent among Ni refinery workers was believed by Kincaid et al. (360) to be $Ni(CO)_4$.

b) Metallic Ni is an important cause of Ni dermatitis. It can also cause a secondary eruption in areas other than the contact site.

c) The authors did not believe that valid conclusions could be drawn relating Ni to blood diseases from available data.

4. In 1968 Peterson (585) reported the case of a woman (38 years old) with eruptions on both her ear lobes and thighs from contact with earrings and garters containing Ni. The author considered Ni the most common sensitivity-producing metal. He noted that contact allergy to Ni was on the increase due to the presence of Ni in alloys of gold and silver used to make jewelry, zippers, buckles and similar articles. Desensitization attempts have thus far been unsuccessful.

III. Long Term Toxicity

A. Mice

1. In 1958, Hueper (285) conducted inhalation experiments with powdered metallic nickel (diam. 4 μ or less). Mice (20 female, C57 Black Strain, 2 months old) were exposed to an atmosphere containing 15 mg Ni/m^3 air six hours/day, four to five days/week for a maximum of 21 months, when all experimental animals were dead.

Necropsy showed the majority of mice had hyperemic and hemorrhagic lungs. The livers were congested. There were no pulmonary neoplasms. (This strain of mice does not develop spontaneous lung tumors.)

2. In 1963, Schroeder et al. (676) studied the effect of Ni and survival of mice fed a diet adequate for growth and reproduction. The purpose of these experiments was to duplicate in mice the tissue concentration of metals found in man and to observe any obvious effects. The authors noted that the only organ in which Ni has been found to increase with age is the lung. Its biological significance, however, is unknown.

The experimental animals, 104 weanling (21 - 23 days old) Charles River CD white mice (50 male and 54 female) were housed in quarters which kept environmental metal contamination to a minimum. They were fed a diet of rye, corn oil and dried skim milk with added vitamins. The concentration of Ni to which they were exposed via diet and bedding was: special diet of 0.4 μg/g wet weight (intake of food per day per mouse was ca. 4x this amount); bedding (softwood chips) 0.32 μg/g wet weight. The Ni was given in the drinking water at 5 ppm divalent Ni (as the acetate salt) for life.

The results were:

a) Mean weights: No significant differences from controls were observed. (See Tables 46 and 47)

b) In terms of survival: All female mice were healthier than males. (See Table 48)

c) Up to 18 months of age, Ni had no obvious effect on mortality. However, when the half-life (time when 50% were dead) of males was compared to controls, Ni decreased it by one to two months.

d) The rate of growth was almost identical to that of controls. (See Figure 5)

Table 46.

Mean Weights of Male Mice Given Nickel (5 ppm in Drinking Water) (676)

Metal	No. of Animals	Body Weight at Indicated Ages		
		60 days	180 days	360 days
		g	g	g
Control	62	35.6 ± 0.38[1]	45.2 ± 1.09[1]	45.1 ± 1.61[1]
Nickel	50	34.9 ± 1.27	45.6 ± 2.05	45.8 ± 2.35

[1]Mean Weight ± SE of Mean.

[2]Probability of Difference Being Due to Chance by Student's t test. Only Significant P Values are Shown.

Table 47.

Mean Weights of Female Mice Given Nickel (5 ppm in Drinking Water) (676)

Metal	No. of Animals	Body Weight at Indicated Ages		
		60 days	180 days	360 days
		g	g	g
Control	88	29.4 ± 0.38[1]	41.0 ± 0.73[1]	46.4 ± 1.20[1]
Nickel	54	29.8 ± 1.45	39.7 ± 2.05	43.7 ± 1.63

[1]Mean Weight ± SE of Mean.

[2]P Indicates Probability of Difference Being Due to Chance by Student's t Test. Only Significant P Values are Shown.

The author concluded from this experiment that in these doses Ni did not affect either mortality or growth. In a later similar experiment (672), however, in which the reproduction of rats was studied, the authors concluded that feeding an element for life was not as sensitive a method for detecting toxicity as a reproductive study since they had been able to show that Ni, when fed in doses which did not affect growth or survival, was intolerable for normal reproduction (see page 38, Section Biology II E5).

Table 48.

Mortality of Mice Given Nickel (676)

Metal Given	No Animals at 2 Months of Age	% Surviving, Months				Half-life (days)
		6	12	18	21	
Male						
Controls	61	96.7	68.8	47.3	35.9	510
Nickel	50	100.0	66.0	38.0	30.0	449
Female						
Controls	88	97.7	93.2	72.7	53.4	662
Nickel	54	100.0	92.4	71.7	57.4	673

[1]P Indicates Probability of the Differences From Controls Being Due to Chance by χ^2 Analysis.
[2]Series Incomplete.

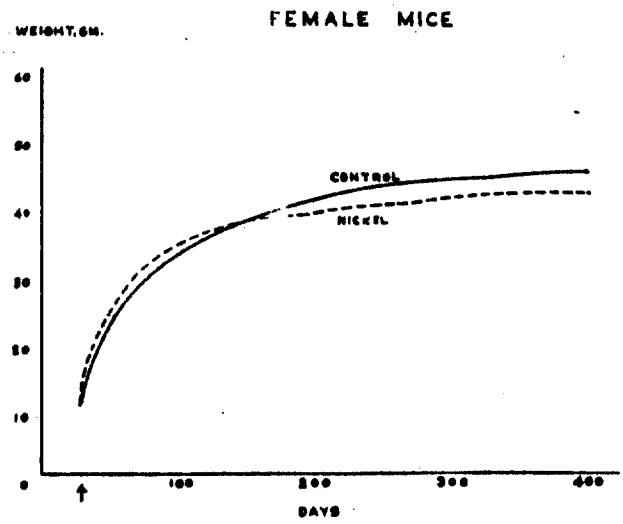

Figure 5 . Curves of Growth of White Mice Given Divalent Nickel at 5 ppm in Drinking Water from the Time of Weaning. Differences were not Significant. (676)

3. In 1964, Schroeder et al. (674) continued studies previously reported (676, page 57) of the effects of small doses of certain trace metals, duplicating human concentrations, on the growth and longevity of mice. This report concerned the total experience for the animals' lifetime with respect to mortality, gross causes of death and tumor incidence (organ accumulation is reported on page 98). The object of these experiments was to reproduce the lifetime human experience by causing accumulations of Ni in mice equal to those of man.

Charles River white Swiss mice (50+ of each sex) were exposed from weaning for their lifetime, to drinking water containing the essential trace metals Mn, Co, Cu, Zn and Mb (for experimental details, see 676) to which 5 ppm divalent Ni (as the acetate salt) was added. The experiment was terminated at 36 months when all the animals died.

Causes of death were divided into four categories: tumors, internal hemorrhage, infection and others plus unknown.

a) Ni was found to reduce visible tumors in the experimental females as compared to controls (see Table 49).

Table 49

Gross Causes of Death in Mice[1] Given Nickel: Significant Differences from Controls (674)

	Controls	Nickel	
	No.	No.	P Value
Males			
Tumors	11(5)[3]	7(4)	
(Lung)	8	5	
Hemorrhage	7	14	
Infection	5	9	
Other and Unknown	21	11	
Total No.	44	41	
Females			
Tumors	22(8)	3(3)	< 0.01
(Lung)	9	3	
Hemorrhage	9	8	
Infection	11	12	
Other and Unknown	18	10	
Total No.	60	33	

1. Autopsied Mice.
2. P = Probability According to Chi-Square Analysis of Differences from Controls Being Due to Chance.
3. Numbers in Parentheses are Deaths from Tumor Before 600 Days of Age.

b) After one year animals of both sexes weighed somewhat less than controls (4 to 13%)

c) Longevity was decreased (see Table 50)

The authors' conclusion was that their experiment demonstrated the "innate toxicity" of Ni to mice at tissue levels within the human range.

Table 50.

Longevity of Mice Given Nickel: Ages at Which 75% Were Dead, Mean Ages at Death of Last Survivors 10%, and Ages of Last Survivors (Days) (674)

	Males				Females			
	No.	75% Dead	Mean Age	Maximal Age	No.	75% Dead	Mean Age	Maximal Age
Control	61	693	957	1035	88	777	966	1084
Nickel	50	623	896	995	54	750	929	1042

B. Rats

1. In 1952, Phatak and Patwardhan (592) studied the general condition and growth of rats fed on a Ni-containing diet for 16 months. The animals, 42 young rats (4 to 5 weeks old) were continuously fed a diet containing 25 mg Ni/100 g diet (a Ni catalyst was mixed with 100 g diet). Six controls were kept on the same diet, Ni-free. The general condition and growth of the experimental rats was comparable to the controls (see Figure 6).

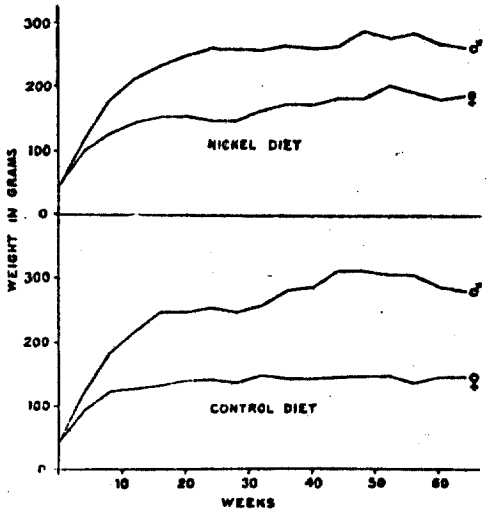

Figure 6 . Growth of Rats on Nickel Diet: 25 Mg. Nickel/100 g Diet (592)

2. In 1957, Sunderman et al. (735) studied the effects produced by long continued exposure of rats to repeated sublethal doses of $Ni(CO)_4$. Male albino Wistar rats were divided into five groups; three groups of 32 animals each (one a control group) average weight 273 g and two groups one with 32 animals and one, a control with nine, average weight 145 g. They were treated as follows: three groups (two 273 g and one 145 g) were exposed to 0.03 mg/liter vaporized $Ni(CO)_4$ dissolved in a mixture of ethyl alcohol and ethyl ether for 30 minutes three times a week for 52 weeks; one group (273 g) exposed first for three weeks to 0.03 mg/liter for 30 minutes three times per week, followed by 0.06 mg/liter for 52 weeks and two groups of controls, one for each treatment, exposed to the alcohol-ether mixture only. At two to three month intervals, randomly selected animals were sacrificed.

The fate of the animals is shown in Table 51, and the weight changes in Figure 7. The authors noted that the high mortality in the control groups was probably due to the alcohol-ether vapor concentration (3 mg/liter) to which all the animals were subjected until it was reduced to about 0.5 mg/liter when the study was 75% complete.

Table 51

Groups of Rats Used in Nickel Carbonyl Studies (735)

Group	Conc. Mg./L.	Initial No.*	Animals Killed	Animals that died †
C_1	0	32	10	11
C_2	0	9	1	5
X_1	0.03	32	4	23
X_2	0.03	32	1	20
Z	0.06	32	9	19

* Surviving animals are being retained and observed for tumor development.

† Several animals listed in this column were killed in a moribund condition.

As can be seen in Figure 7 , the experimental animals did not grow as well as the controls. The experimental animals also showed:

a) Extensive inflammatory lesions in the lungs.

b) Significant increases in the weights of the heart, lungs and adrenals.

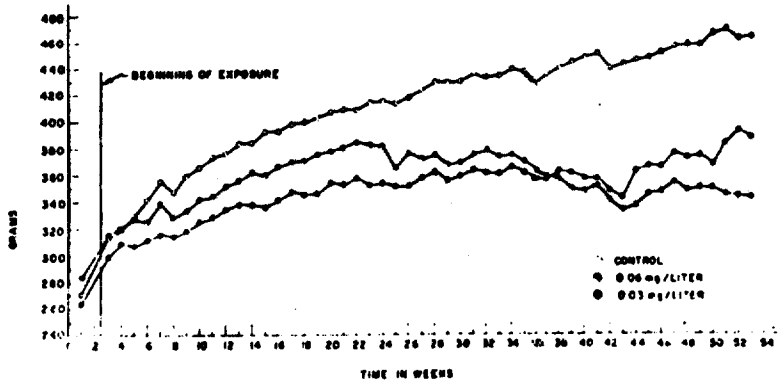

Figure 7. Weight Curves of Rats Exposed to Nickel Carbonyl (735)

The authors concluded that there was little doubt that chronic exposure to $Ni(CO)_4$ impaired the health of rats.

3. In 1965 Sunderman and Donnelly (729) compared the mortality data and weights of rats exposed to $Ni(CO)_4$ to that of unexposed animals. Wistar strain, male white rats (64, 200 - 250 g) were exposed for their lifetime to 4 ppm (0.03 mg/l) $Ni(CO)_4$ vapor for 30 minutes daily three times per week. The controls (32) inhaled alcohol-ether vapor 30 minutes a day, three times per week for their lifetime. After three weeks, all the animals in both groups were alive.

The results with respect to mortality and growth are shown in Figures 8 and 9. From the mortality curve, it can be seen that the mortality of the experimental animals after two years was about three times greater than that of controls.

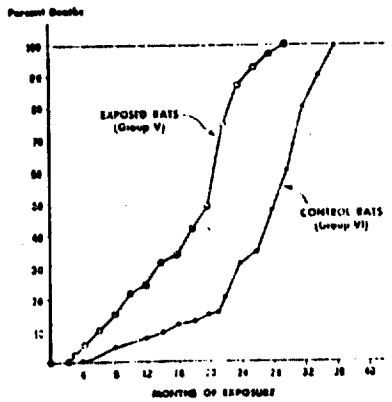

Figure 8 . (729)
Chronic Exposure of Rats to Nickel Carbonyl
(4 parts per million -
3 times weekly until death)
(Death curves)

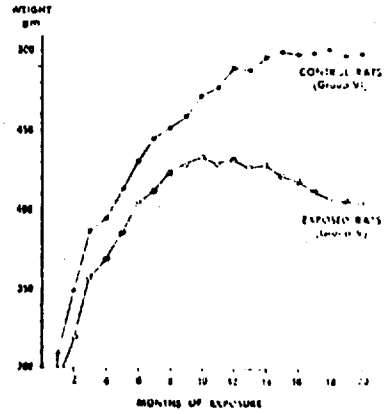

Figure 9 . (729)
Chronic Exposure of Rats to Nickel Carbonyl
(4 parts per million -
3 times weekly until death)
(Weight curves)

Death rate, according to the figures, showed:

a) By the end of the first year; 25% to 7%.

b) By the end of the second year; 88% to 30%.

c) The last experimental rat died 29 months after initial exposure and the last control rat died at 36 months.

From the weight curve, it can be seen that throughout the entire three-year period of the study, the mean weight of the experimental animals was less than that of the controls.

4. In 1974, Schroeder et al. (675) exposed rats to Ni in drinking water for life. (The environmental conditions for the experiment are described in 676 .) At weaning, 104 rats (Long-Evans BLU:(LE) strain, 52 male and 52 female) were put on a diet adequate for growth and survival (see original paper of diet), and given basal water (described in original paper) plus 5 ppm Ni for life. The controls, 52 male and 52 females (same strain) were given the diet and basal water for life. The results are summarized in Tables 52, 53, and 54, which show:

a) Rates of Growth (Table 52): Ni apparently enhanced growth of the males at four age-intervals up to six months and at two age-intervals for the females. At 18 months, Ni-fed rats were smaller than controls.

Table 52.

Weights of Rats Given Nickel (675)

Age, days	Control-3	Nickel
Males		
30	61±2.9[1]	68± 4.3
60	174±4.6	199± 7.3[2]
90	229±4.4	253± 8.1[2]
120	264±6.8	311± 9.2[2]
150	307±4.9	341± 9.6[4]
180	334±5.7	348±10.8
360	398±5.4	400±10.3
540	456±7.9	397±16.8[4]
Females		
30	70±2.6[2]	68± 3.5
60	150±3.9	158± 4.5
90	178±6.2	196± 4.3[2]
120	203±5.9	219± 5.7[4]
150	221±6.7	221± 5.1
180	234±6.2	229± 6.3
360	253±4.0	258±11.2
540	261±6.4	236± 8.4[3]
Intake, Ni, μg/g	0.44	5.44

[1] ±s.e.m. [2] Differs from preceding group at comparable age, $P < 0.01$. [3] $P < 0.001$. [4] $P < 0.005$. [5] $P < 0.025$. [6] $P < 0.05$.

b) Life Spans (Table 53): There was no significant difference between Ni-fed and control rats.

Table 53.

Life Spans of Rats Given 5 ppm Nickel (675)

Metal	No. rats	50% dead	75% dead	90% dead	Last survivor	Longevity[1]
				days		
Males						
Control-3	52	853	1004	1090	1160	1118±17.3
Nickel	52	857	952	1120	1162	1122±10.2
Females						
Control-3	52	872	1022	1149	1234	1177±28.4
Nickel	52	924	1070	1120	1346	1217± 7.4

[1] Mean ±SEM of last surviving 10%. Differences were not significant.

c) Tumors (Table 54): No excessive number of gross microscopic or malignant tumors appeared in Ni-fed groups as compared to controls.

Table 54.

Gross and Microscopic Tumors in Rats Given Nickel for Life[1] (675)

Metal	No. autopsied	Tumors		Sectioned	Tumors		Malignant	
		No.	%	No.	No.	%	No.	%
Males								
Control-3	40	13	32.5	23	9	39.1	4	17.4
Nickel	26	10	38.5	17	4	23.5	2	11.8
Females								
Control-3	35	18	51.4	26	10	38.5	7	26.9
Nickel	36	19	52.8	27	9	33.3	3	11.1

[1] There were no significant differences between controls and treated groups.

d) The only specific lesion seen in microscopic section was a slightly increased incidence of focal myocardial fibrosis (13.3%) in Ni-fed rats as compared to controls ($P < 0.025$).

The authors concluded from their data that when given for life to rats at 5 ppm, Ni was non-toxic.

IV. Special Studies

Cancer

A. In Vitro

1. In 1968, Swierenga and Basrur (747) examined the effect of Ni on mitotic cells and spindle proteins. They were testing whether cell division was inhibited by the primary interaction of Ni with -SH groups because these groups were assumed to be involved in the control of cell division and tumor induction. Three series of experiments were carried out:

a) Cultures were set up from the limb muscle of 16- to 20-day old rat embryos and treated when one-day old with 0.2 ml prepared Ni solution (powdered nickel sulfide mixed into phosphate-buffered saline) at a concentration of 1.0 µg Ni/ml culture medium. Mitotic indices were determined for experimental and control cells.

b) To evaluate the influence of the age of cultures at the time of treatment cultures were exposed to the Ni solution starting with the first day after explantation and exposure to Ni was kept constant for 24 hours.

c) The spindle apparatus was studied by treating 24-hour old cultures with the Ni solution for 24 and 48 hours.

The results of these experiments are summarized in Tables 55 and 56 , and Figure 10.

Table 55.

Cell Counts and Mitotic Indices of Untreated and Nickel-Treated Rat Embryo Muscle Cultures (747)

Age of cultures at harvest	Untreated		Treated		
	No. of cells per field	Mitoses	Duration of treatment[a]	No. of cells per field	Mitoses
hr.	*mean*	%	*hr.*	*mean*	%
48	46	2.4	24	52	1.3
72	76	2.9	48	36	1.4
96	120	3.1	72	55	1.3

[a] Cultures were 24 hours old at the commencement of nickel treatment.

Table 56.

Frequency of Abnormal Mitoses in Untreated and Nickel-Treated Rat Embryo Muscle Cultures (747)

Age of cultures analyzed	Duration of treatment	Types of abnormal mitoses				Total abnormal mitoses
		Tripolar	Tetra-polar	C-mitoses	Laggards	
hr.		%	%	%	%	%
48	Control	0	0	1.3	8.4	9.7
96	Control	1.1	0	1.0	7.0	9.1
48	24 hr.	7.1	2.0	3.0	13.5	25.6
96	48 hr.	12.5	0	0	18.0	30.5

The authors concluded that the most significant effects of Ni on rat embryo muscle cultures were the suppression of division in a majority of cells and the production of aberrant mitoses.

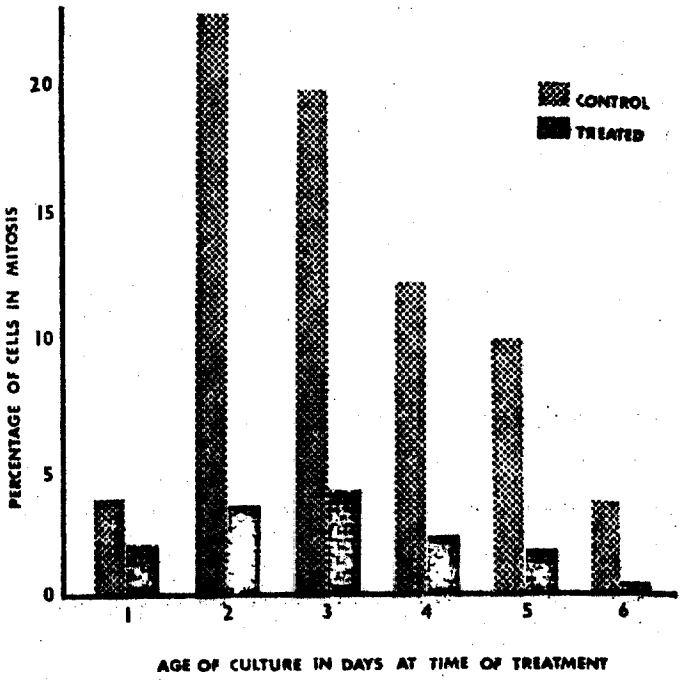

Figure 10. Histogram Showing the Mitotic Index in Nickel-Treated and Control Rat Embryo Muscle Cultures. Each Set of Cultures was Exposed to Nickel Starting From the First Day of Explantation for 24 hours, Including 6 Hours With Colchicine. (747)

2. In 1971, Sykes and Basrur (748) continued their investigations reported above (747) by studying the ultra-structural features of nickel-treated and untreated myoblasts. Exposure of cultures to nickel sulfide (known to induce muscle tumors in rats when given i.m.) for 24 hours caused the destruction of a majority of mononucleate cells while the surviving cells exhibited a variety of alterations in cell organelles. The authors concluded that the observed blebbing and elimination of cytoplasm might be related to the dedifferentiation which generally takes place in the reactive zones where muscle cells and straps are seen to be reverting to mitosis during tumorigenesis.

B. Insects

In 1960, Kanehisha (323) investigated whether there was any relation between metal accumulation and melanotic tumor formation in Drosophila melanogaster. Pupae of both tumor and non-tumor strains were used in the study. (See original paper for experimental details.)

It was found that Ni incorporation was relatively higher than iron incorporation in melanotic tumor formation. The authors concluded that their experiments suggested an intimate relation between Ni and tumor formation.

C. Mice

In 1962, Gilman (215) studied the comparative tumorigenic activities of metal compounds isolated from refinery dust. Two of these, nickel sulfide (Si_3S_2) and nickel oxide (NiO) found to be tumorigenic to rats were tested with two different strains of mice, C3H and Swiss (two to three months old).

Single i.m. injections (5 mg per thigh) of suspensions of the powdered nickel compounds were administered to equal numbers of both sexes. The experiment, treatment and tumor response is summarized in Table 57.

Table 57.

Carcinogenicity of NiO and Ni_3S_2 On Intramuscular Injection Into C3H and Swiss Mice (215)

Treatment				Tumor response					
Metal	Strain and no. mice	Total sites injected	Dose/ site (mg.)	No. tumor animals	Per cent affected sites	Av. latent period (days)	Av. progr'n time (days)†	Duration of exp. (days)	Survivors at end of exp.
Ni_3S_2	Swiss-45	51*	5	27	53	250	131	478	8
	C3H-18	30	5	9	33	225	139	448	2
NiO	Swiss-50	100	5	33	35	287	78	476	4
	C3H-52	104	5	23	23	256	71	476	8

* Only a few Swiss mice were injected in both thighs with Ni_3S_2, owing to its toxicity.
† Average number days from appearance of first tumor to death.

The results showed that:

a) Both nickel compounds were equally tumorigenic as evidenced by average latent period and numbers of tumor-bearing animals.
b) All the tumors were sarcomas.
c) There was no sex difference but there was a strain difference C3H being more refractory than Swiss based on percent tumor response.
d) Tumor response in rats was higher than in mice (see this Section D6, page 73).

The author noted that the consistently lower tumor response of C3H strain mice as compared to Swiss mice to nickel compounds, was probably due to general or systemic tumor resistance as opposed to a specific refractoriness of local tissues to the carcinogenic agent.

D. Rats

1. In 1951, Hueper (282) reported the results of injecting rats i.p. with nickel powder. Seventy rats were divided into three groups and injected with Ni as follows:

a) 0.05 cc of a 25% suspension by volume in lanolin in the femoral cavity of 25 rats.
b) Five injections of the same suspension in the right pleural cavity of 25 rats.
c) Two injections of 0.1 cc of a 12.5% suspension in the nasal sinuses of 20 rats.

The results were:

a) Fifteen died within the first 6 months without neoplastic reactions.
b) Ten of the 24 rats which died within 7 - 14 months showed sarcomatous growths at the injection site of spindle-cell, round-cell and giant-cell structure.
c) Several cases had metastases.

2. In 1952, Hueper (283) repeated the experiment reported above (282) in which pure metallic nickel powder suspended in lanolin was administered to rats

by three different parenteral routes. Six-month old female rats, Osborne Mendel strain, were divided into three groups:

a) Intrafemoral route: About 0.05 cc of a suspension of Ni powder in lanolin (50 mg Ni, 12.5% by volume and 61% by weight) was injected into the right femur of 25 animals.

b) Intrapleural route: At five monthly intervals about 0.05 cc of the same Ni suspension was injected into the right pleural cavity of 25 animals.

c) Intranasal sinus route: Three injections at two-month intervals of 0.1 cc of the suspension (12.5% Ni by volume; 43.8% by weight) was introduced into the right sinuses of 20 four-month old animals.

The experimental observations were (see Table 58):

a) Among 30 rats dying between 7 to 16 months, there were 10 malignant tumors and 6 osteogenic sarcomas - one originating from connective tissue at the injection site, one from the epithelial lining of an osteomyelitic fistula, and two from abdominal lymph nodes.

b) The site of the cancer in eight of these was closely related to the Ni deposit produced.

c) Histologic examination showed that in several cases, the Ni deposits were proximal to the malignant growths.

d) The minimum latent period was about six months.

The author concluded that the evidence strongly suggested that finely dispersed metallic Ni might elicit cancerous reactions in contacted tissues.

Table 58

Neoplastic Responses in Rats After Nickel Injections (283)

Route	No. Rats	Deaths 0-6 months	Deaths 7-16 months	Tumor at Site of Inj.	Tumors remote from site
Femur	25	2	17	4	1
Pleura	25	8	10	4	0
Nasal Sinus	20	6	3	0	1

3. In 1955, Hueper (284) continued his investigations of the carcinogenicity of metallic Ni. To mitigate any special strain-specific influence, Wistar strain rats were used in this experiment (Osborne Mendel strain animals were previously used).

About 0.1 cc of a 5% Ni suspension (about 50 mg Ni) in 20% gelatin-saline solution was implanted in the narrow cavity of the right femur in two groups of 50 rats each (3 months old, both sexes). One group of rats received powdered metallic Ni with irregular shaped, ragged particles, 2 to 50 microns in diameter (CAC), while the other received Ni made up of minute round particles clumped together (INCO).

The results, summarized in Table 59, were:

a) Tumors at the site of Ni implantation first appeared after a 4 to 5 month induction period.

b) There was a total of 27 cancers of different histogenetic origin among both groups of rats.

c) There were 20 additional tumors, both malignant and benign, found in sites remote from the Ni implantation.

d) The 23 seven-month old female Wistar rats used as controls which were similarly injected with 0.1 cc of the gelatin-saline vehicle, did not develop tumors of the right thigh. They did, however, develop 10 benign or malignant neoplasms. (See Table 60, for survival rates of controls and page , this section F for similar experiment with rabbits.)

Table 59.

Survival Periods and Tumor Formation in Thighs of Rats After Intrafemoral Deposition of Nickel (284)

Months.....	1-3	4-6	7-9	10-12	13-15	16-18	19-24	25-28	Total
Deaths INCO.....	1	9	2	3	3	12	11	9	50
Deaths CAC.....	.....	5	7	5	3	10	10	10	50
Tumors INCO.....	.....	5	.....	2	.....	1	5	1	14
Tumors CAC.....	.....	1	5	1	.....	2	3	1	13

Table 60.

Survival Periods of Rats Intrafemorally Injected With Gelatin Solution (282)

Months.....	4-6	7-9	10-12	13-15	16-18	19-21	22-24
Deaths.....	2	3	1	0	2	5	10

4. In 1958, Hueper (285) studied the carcinogenicity of inhaled nickel powder. The test animals, 100 Wistar rats (equal number of both sexes) and 60 female Bethesda Black rats, were exposed six hours per day for four to five days per week for a maximum of 21 months (when all animals had died) to 15 mg powdered Ni/m^3 air.

It was observed that about 50% of both strains of rats developed abnormal multicentric adenomatoid formations affecting the alveolar structures, as well as atypical proliferations of the epithelial lining of the terminal bronchioli. (See also page 87, this Section E.)

The author concluded that the benign hyperplastic adenomatoid proliferations in the rats' lungs were attributable to the inhaled Ni dust, which duplicated the conditions associated with the occurrence of cancers in various parts of the respiratory tract of nickel workers (nasal cavity, nasal sinus, lung) and that in both the rat and human, these are reactions of the respiratory tract to inhaled Ni.

5. In 1959, Sunderman et al. (734) continued their investigations of $Ni(CO)_4$ as a possible carcinogenic agent which were originally prompted by the high incidence of respiratory tract cancer among long-time workers with this compound.

Two groups of animals were exposed for 30 minutes, three times weekly for one year to two different concentrations of $Ni(CO)_4$. (See Table 61.) At the end of the year, 14 controls and 20 test animals survived. A third group of 80 rats was exposed only once to $Ni(CO)_4$ at a concentration approximating the LD_{50} value (See Table 61.)

Four of the nine test animals which survived two or more years after initial exposure, developed tumors; one from group X, one from group Z, and two from group EP (see Table 61).

The authors concluded that inhalation of $Ni(CO)_4$ could cause pulmonary cancer in the resistant rat lung.

Table 61.

Exposure Data (734)

Rat Group	$Ni(CO)_4$ Dosage * Concentration, Mg/L.	Exposure	Initial No.	Deaths During Months † 0-12	13-24	25-?
C	0.0 ‡	3X weekly-1 year	41	27	11	3
X	0.03	3X weekly-1 year	61	48	11	2
Z	0.06	3X weekly-1 year	32	28	3	1
EP	0.25	single exposure	80	72	5	3

* Vaporized from a solution of $Ni(CO)_4$ dissolved in mixture of 50% alcohol and ether.
† Includes rats killed + spontaneous deaths.
‡ Exposed only to vaporized alcohol-ether vehicle.

6. In 1962, Gilman (215) studied the comparative tumorigenic activities of metal compounds isolated from refinery dust. Suspensions of three powdered Ni compounds; $NiSO_4 \cdot 6H_2O$, NiO and Ni_3S_2 were injected i.m. in a single 20 mg dose into both the left and right thigh muscles of each rat, 32 rats per compound. The experimental details and results are summarized in Table 64.

The results showed that:

a) Tumors developed at site in 89% of Ni_3S_2 treated animals; in 66% of the NiO treated animals and in none of $NiSO_4 \cdot 6H_2O$ treated animals.

b) The average latency period for NiO (302 days) to induce a palpable tumor was significantly longer than for Ni_3S_2 (150 days).

c) Metastases were observed in almost all Ni_3S_2 treated animals autopsied (see Table 63).

d) The difference in tumor progression time (rapidity with which induced tumors caused death) between animals with Ni_3S_2 and NiO induced tumors, 28 days, was significant ("t" = 2.219, df = 34, $P < 0.05$, (see Table 64).

The author concluded that Ni_3S_2 was probably the compound responsible for the carcinogenic activity of the metallurgical dust sample (collected from the dust flue of a nickel refinery) originally investigated. (See this Section C1, page 68.)

Table 62.

Local Tumor Response of Rats to Single Intramuscular Injections of Metallurgical Compounds (215)

Group Number and Compound	Number on Experiment	Effect. no. Rats	Total Inject. Sites	Total Tumors at Site	Number Tumor Rats	Days to 1st Tumor	Average Latent Period (days)	Days on Experiment	Survivors at End Experiment	Miscellaneous Tumors
$NiSO_4 \cdot 6H_2O$	32	27	54‡	0				603	13	1 Lymphona 1 Uterine Fibroma 4 Mam. Fibroadenomas
NiO	32	32	64	26][	21	180	302][	595	5	1 Mam. Fibroadenomas 1 Lymphoma
NiS_2	32	28	45§	36][	25	91	150][	365	0	

‡ 5-mg dose/thigh.

§ Seventeen rats treated in both thighs, eleven in one thigh only.

][Differences significant at 1 per cent level

Table 63.

Frequency and Distribution of Metastases in Induced Rat Tumors (Mostly Rhabdomyosarcoma) (215)

Carcinogen	No. rats autopsied	Metastases		Distribution		
		No.	Per cent	Lung and lymph nodes	Lung only	Lymph node only
Nickel sulfide	21	20	95	14	2	4
Nickel oxide	20	7	35	3	2	2

Table 64.

Comparison of the Average Time From First Appearance of Tumor Till Death in Rats Exposed to Two Carcinogenic Metals (215)

Carcinogen	No. rats	Av. progression time (days)	Difference (days)
Nickel sulfide	20	55	
Nickel oxide	16	83	28*

* Significant at the 5 per cent level.

7. In 1962, Hueper and Payne (287) modified their investigations of the carcinogenicity of metallic Ni by injecting it directly into rats' lungs.

Injection of about 0.02 cc Ni powder suspended in 10% gelatin solution (2g Ni/10 cc 10% gelatin) was made into the right lung of 34 Bethesda black rats (20f, 14m, 3 months old). The procedure was repeated 12 months later with the surviving rats (25% died in the first 72 hours). The maximal observation period was 24 months.

The results of the experiment are summarized in Table 65. Of the three tumors produced, the one involving the right lung was a spindle-cell carcinoma, and the other two were squamous cell carcinomas (of the uterine endometrium and of the skin of the cheek).

Table 65

Death Distribution and Tumor Yield in Rats Following an Intrapulmonary Deposition of Metallic Nickel (287)

	Months							Tumors		
	0-6	7-9	10-12	13-15	16-18	19-21	22-24	Benign	Malignant	Cancers at Site
Rats	8	2	1	4	5	4	10	0	3	1

The authors concluded that the carcinogenic property of metallic Ni was confirmed by the lung sarcoma; the experiment was unsucessful in producing bronchiogenic carcinomas.

8. In 1964, Herchen and Gilman (265) established the approximate exposure time necessary for Ni_3S_2 to cause malignant change in muscle tissue. Solid disks of pressed Ni_3S_2 powder (8 mm x 1 mm, ca. 250 mg) were implanted in the right gluteal region of Fischer rats (15 for each exposure time) for eight exposure periods: 2, 4 8, 16, 32, 64, 128 and 256 days. As a control, an equal-sized disk of ferric oxide (Fe_2O_3) was implanted into the opposite hip.

The observed tumor incidence is summarized in Table 66. No tumors developed at the Fe_2O_3 implantation sites. The authors concluded that for exposure to Ni_3S_2 the critical period of carcinogenic action necessary for malignant change in muscle tissue occurred sometime after 32 days.

Table 66

Effect of Duration of Exposure to Nickel Sulphide Disks on Tumor Incidence (265)

	Days to removal of Implants					
	2; 4; 8; 16	32	64	128	256
No. of effective animals*	10	10	9	10	10	10
Palpable tumors	0	0	4	7	10†
Average latent periods (days)	-	-	191	205	230
Range of latent periods (days)	-	-	171-242	169-265	183-256

* Animals surviving longer than the shortest latent period encountered.
† Not randomly selected (see text).

9. In 1964, Gilman (216) summarized the data on muscle tumorigenesis in rats produced by nickel compounds.

a) The induction of rhabdomyosarcomas with N_3S_2 in millipore diffusion chambers demonstrated that direct contact between carcinogenic metal particles and cells was not essential.

b) The rate of induction or proportion of induced muscle tumors was independent of the physical shape or size of the metal implant (see Table 67).

Table 67

Effect of Physical Shape of Implant on Tumor Response (216)

Type of implant	Tumour rats / Rats on exp.	Average latent period (days)	Tumour distribution Rhabdo.	Fibro.	No histol.
Diffusion Chamber + 10 mg Ni_3S_2	14/17	305*	9	3	2
Ni_3S_2 Disc (11 mm diam.)	14/17	148	12	2	—
Ni_3S_2 Chips (0.3 – 0.5 mm)	5/7	149	4	—	1
Ni_3S_2 Powder – 10 mg (5μ size)	20/20	167	15	2	3
Ni_3S_2 Powder – 10 mg (2μ size)	19/20	170	15	3	1
Diffusion Chamber (Empty)	1/19*	460*	—	1	—
Fe_2O_3 Disc (11 mm diam.)	0/20	—	—	—	—

* Significant difference (1% level).

c) There was a variation in response to tumorigenic Ni compounds both among different rat strains and between species (see Table 68).

d) Regardless of the strain, Ni_3S_2 was the most active metallic carcinogen for the rat.

e) The author's findings with the Ni compounds examined (see Table 69) supported the generality that the more soluble the Ni compound, the greater its toxicity and the less its carcinogenicity. The author considered it probable that metallic Ni itself was the active carcinogenic agent.

Table 68

Tumor Response to Different Nickel Compounds Within and Between Species (216)

Species	Comp.	No. on Expt.	% Tum. Bearers	A.L.P.* (days)	A.P.T.† (days)	Tumour Distribution Rhabdo.	Mes. T.‡	Fibro.	Others§	No histol.
Mice (Swiss)	Ni_3S_2	45	60	251	132	2	3	14	2	6
	NiO	50	66	287	78	5	7	16	1	4
Rats (Wistar)	Ni_3S_2	30	83	150	55	19	2	0	1	3
	NiO	32	65	302	83	14	2	4	0	2

* A.L.P. = Average of Latent Periods in days from time of implantation to appearance of first tumor in each tumor bearing rat.

† A.P.T. = Average of Progression Times in days from appearance of first tumor until death of each tumor bearing rat.

‡ Mes. T. = Mesenchymal tumor-undifferentiated sarcoma of uncertain classification.

§ Others = Most frequently reticulum cell sarcomas (spontaneous mammary tumors were not included here).

Table 69

Relative Solubility and Tumorigenic Activity of Several Compounds of Nickel (216)

Nickel compounds	Tumourigenic activity		
	Fischer rats (6 mo.+ exposure)		Bethesda B1 (22 mos.)
Relative order of solubility	No. tumours / Sites	Per cent tumour bearing rats	Tumour induct. per cent (Payne)*
Ni sulphate	0/54	0	0
fluoride	3/36	17	—
monosulphide	0/28	0	—
acetate	—	—	7
carbonate	—	—	40
hydroxide	19/40	75	—
oxide	2/40	10	8
sulphide	22/40	85	74

* W.W. Payne, 1964, Proceedings 55th Ann. Meeting Amer. Assoc. Cancer Res. (Abstr. No. 197).
W. W. Payne - personal communication

f) With implanted Ni_3S_2 the preponderance of rhabdomyosarcomas arose with subcutaneous and intra-abdominal implantations (see Table 70). Foreign body granulomas were caused by intraperitoneal and intrasplenic implants of powdered Ni_3S_2.

Table 70

Effect of Implantation Site of Ni_3S_2 on Tumor Class and Incidence (216)

Implant site	No. tum. Sites	Per cent T.	Tumour classification Rhabdo.	Mes. T.	Fibro.	Other	No histol.
Intramuscular	32/40	80	25	2	2	0	3
Subcutaneous	28/64	44	16	4	3	1	4
Intraperitoneal	9/37[a]	24	8	1	0	0	0
Intrasplenic	4/20[b]	20	1	0	1	1	1

[a] 4 of the 9 animals developed muscle tumor involving abdominal wall and/or diaphragm.
[b] Experiment still in progress.

g) Ni-induced rhabdomyosarcomas metastasized freely via both the lymphatic and blood streams.

h) Preliminary findings on the effect of CaEDTA on Ni_3S_2 tumorigenesis indicated that tumorigenesis was considerably inhibited by blocking the metal availability via chelation (see Table 71).

Table 71

Effect of CaEDTA on Nickel Tumorigenesis (216)

	No. tum. Sites	(%)	ALP (days)	Survivors (23 mos.)
Ni_3S_2 discs (11 mm)	7/8	88	132	0
Ni + CaEDTA (1:9)	4/8	50	309	2
Ni + CaEDTA (1:19)	2/8	25	373	2
CaEDTA (control)	0/8	—	—	3

10. In 1965, Payne (577 and author's unpublished data) investigated whether carcinogenicity of Ni compounds was dependent on their solubility or valence state. Pellets made with sheep fat of nine Ni compounds (7 mg) with various solubilities were surgically implanted three times into the muscle tissue of nine groups, 35 in each, adult male and female Bethesda Black rats (NIH colony). Controls were implanted

with pellets of sheep fat. The compounds tested, their solubilities, tumors produced and survivals are shown in Tables 72 and 73 in unpublished paper.

Table 72.*

Induced Tumors in Rats / Survivors at Specific Intervals

Compound	Months						Tumor Induction Percentage (20 mos.)
	6	9	12	15	18	20+	
Nickel Sulfide	0/35	0/32	0/30	6/24	11/17	22/5	74
Nickel Carbonate	0/35	0/32	1/30	2/25	6/17	10/10	40
Nickelous Oxide Green	1/34	1/33	1/32	1/23	4/17	4/13	18
Nickelic Oxide	0/33	0/33	0/33	0/29	0/26	1/22	8
Nickel Acetate	0/35	1/33	1/33	1/31	1/28	1/20	7
Nickel Acetate Anhyd.	0/34	0/33	0/31	0/27	0/20	1/14	5
Nickel Ammonium Sulfate	0/35	0/32	0/32	0/29	0/26	0/18	0
Nickel Sulfate	0/35	0/35	0/35	0/32	0/29	0/25	0
Nickel Chloride	0/35	0/35	0/34	0/29	0/28	0/26	0
Controls	0/35	0/31	0/29	0/24	0/19	0/18	0

*W. W. Payne - Author's Unpublished Data, 1965.

The observations after 18 months were:

a) Ni sulfide: 12 animals developed tumors at site, 8 died without tumors, 15 survived

b) Ni carbonate: 6 animals with tumors, 12 without tumors, 17 survived.

c) Ni (II) oxide: 4 animals with tumors, 14 without tumors, 17 survived.

d) Ni sulfate and acetate: single tumors.

e) Ni chloride, anhydrous acetate, ammonium sulfate, Ni (III) oxide and controls: no tumors.

f) Histological: tumors were rapidly growing anaplastic sarcomas with some metastases.

g) The soluble compounds (see Table 73) were more toxic and excreted more rapidly in the urine and feces.

The author concluded that both the valence state and solubility of Ni compounds were related to their carcinogenicity.

Table 73.**

Number of Tumors at Site and Solubility of Nickel Compounds

Nickel Compound	No. tumors at site	Solubility in Saline, 37°C
Sulfide	22	< 1.0 µg/ml
Carbonate	10	22.6 µg/ml
Oxide Green	4	3.1 µg/ml
Oxide	1	1.0 µg/ml
Acetate, anhyd.	1	120.0 mg/ml
Acetate	1	238.0 mg/ml
Ammonium Sulfate	0	*392.0 mg/ml
Sulfate	0	762.0 mg/ml
Chloride	0	1256.0 mg/ml

*From Handbook of Chemistry

**W. W. Payne - Author's Unpublished Data, 1965.

11. In 1965, Heath and Daniel (255) investigated the carcinogenic effects of pure Ni powder. Pure Ni powder (0.0283 g) suspended in 0.4 ml fowl serum was injected into the right thigh muscle of 10 Hooded strain female rats (two to three months old). Previous studies had shown fowl serum produced no reactions or tumors.

The observations were:

a) No clinical evidence of an immediate toxic response.

b) All the animals developed tumors clearly originating in the striated muscle at the injection site.

c) The latent period was from 17 to 22 weeks.

d) Three animals developed metastases in the prevertebral lymph nodes.

The authors concluded that powdered Ni injected i.m. into rats produced well differentiated tumors originating in striated muscle.

12. In 1965, Sunderman and Donnelly (729) continued their studies on nickel carcinogenesis in which white rats (Wistar strain, male, 200 - 250 g) inhaled $Ni(CO)_4$ vapor (for exposure concentration, mortality and tumors (see Table 74).

Table 74.

Pulmonary Cancer with Metastases in Rats Exposed to Nickel Carbonyl (729)

Type of exposure	Concentration of $Ni(CO)_4$ in parts per million	Death of rats months after initial exposure	Type of tumor
3 times weekly for 1 year	4	24	Squamous cell carcinoma
3 times weekly for 1 year	4	24	Squamous cell carcinoma
3 times weekly for 26 months	4	26	Adenocarcinoma
Single exposure	35	27	Anaplastic carcinoma
Single exposure	80	24	Adenocarcinoma
Single exposure	80	26	Anaplastic carcinoma

The pulmonary carcinomas with metastases listed in Table 74, developed in 6 of 89 rats surviving two or more years after initial exposure to $Ni(CO)_4$. In another

experiment, 3 of 80 rats surviving beyond the two-year latent period after exposure to $Ni(CO)_4$ developed pulmonary carcinoma with metastases.

The authors noted that:

a) Rat lungs were peculiarly resistant to primary pulmonary carcinoma.

b) Over a period of 12 years, they had never encountered carcinoma of the lung in an untreated control rat and none had been reported in the literature.

c) Six rats exposed to $Ni(CO)_4$ were found to have pulmonary carcinomas with metastases in a combined series of studies.

The authors concluded that inhaled $Ni(CO)_4$ was carcinogenic to the lungs of rats, a species generally considered to be peculiarly resistant to pulmonary cancer.

The authors further related their observations to Ni exposure in cigarette smoke as follows:

a) Earlier studies (cited in original paper) had shown that carcinoma of the lung developed in rats which inhaled $Ni(CO)_4$ three times weekly for one year (about 1930 µg Ni total dosage).

b) The total dosage inhaled by these rats was equivalent to the amount of Ni contained in the main stream smoke of about 26 packs of cigarettes (0.37 µg Ni/cigarette).

c) The amount of Ni capable of inducing lung cancer in the rat in comparable to the amount inhaled by smokers from less than 15 cigarettes/day for one year.

13. In 1966, Daniel (147) investigated the resistance of three rat strains -- Hooded, Fischer and Bethesda Black -- to i.m. implanted Ni_3S_2 to confirm the findings of Gilman (page 73, 215) that a high incidence of tumors developed in Hooded or Fischer rats as contrasted to Payne (page 79, 577) who found Bethesda Black rats relatively resistant.

In the first experiment, the relative sensitivities of two strains of rats were studied by injecting i.m. into each gastrocremius of each rat, 0.1 ml Ni_3S_2 suspended in aqueous penicillin G procaine (100 mg Ni_3S_2/ml). In the Hooded, 15 male and 15 female, and in the Bethesda Black, 15 male and 12 female were used.

The results are summarized in Table 75. Some of the observations were:

a) Bethesda Black rats were less susceptible than Hooded to the carcinogenic action of Ni_3S_2.

b) Tumors were produced in all the Hooded but only in 14 of the 27 Bethesda Black rats.

c) Almost all Hooded rats developed tumors at the injection site in both legs. In the Bethesda Black only one leg was affected and the average latent period was twice as long.

In a second experiment to compare the short-term response of the muscle tissue, 5 males and 10 females of the Hooded and Bethesda Black strains and 10 of each sex in the Fischer strain, were treated as in the first experiment. After injection samples of both sexes were sacrificed at two-week intervals.

The most striking difference among the three strains of rats was the massive phagocyte invasion at the injection site of the most resistant strain, Bethesda Black. These phagocytes ingested the carcinogen without apparent damage.

The author concluded that in confirmation of Payne's results, the Bethesda Black strain is more resistant than the Hooded strain to the carcinogenic action of Ni_3S_2.

Table 75.

Tumor Production in Hooded and Bethesda Black Rats in Response to Intramuscular Injection of Nickel Sulphide (147)

Strain	Sex	Proportion of rats with tumours	Number of tumours	Period for development of visible tumour (weeks)	Number of tumours containing						
					Rhabdomyosarcoma				Fibrosarcoma	Reticulum cell sarcoma	Other components
					[2] Poor	Fair	Good	Very good			
Hooded	♂	15/15	28	17-26	4	6	17	0	4	1	0
	♀	13/13	26	16-22	2	7	15	2	1	2	1 (Haemangio-sarcoma)
Bethesda Black	♂	7/13[1]	7	23-57	4	2	0	1	3	4	1 (Lympho-sarcoma)
	♀	7/10	7	19-56	1	4	0	0	3	3	0

[1] The total numbers of male and female Bethesda Black rats are those at the conclusion of the experiment (14 months after injection).
2 rats of each sex, killed at 4½ and 10 months after injection, were tumour-free.
[2] Degree of differentiation.

14. In 1967, Heath and Webb (257) studied the distribution of the inducing metal in the resulting primary tumors. A suspension of finely powdered Ni (28 mg) in horse serum was injected into the thigh muscle of Hooded rats (2 to 3 months old) to induce primary tumors.

A total of 22 tumors were induced by Ni. The metal ion (Ni^{2+}) was also detected in a lymph node tumor that developed, probably as a metastasis, in one animal.

It was observed that:

a) The content of metal,incorporated in each tumor decreased both from the center to the periphery and with the age of the tumor, as the implant dissolved and was eliminated from the implantation site.

b) Most of the metal which was incorporated intracellularly by the primary tumors was bound by the nuclear fraction at least part of which was due to binding by the nucleic acid.

c) Smaller amounts were present in the mitochondrial and soluble fractions with little or none in the microsomes.

d) Transplants of these tumors neither concentrated nor needed Ni cations in excess of any normal requirements for growth and survival.

15. In 1968, Haro and Furst (246) reported on induction of tumors with nickelocene, a new pi-complex of nickel dicyclopentadiene. Intramuscular injections were given monthly to Fischer - 344 rats of trioctanoin suspensions of nickelocene (50 mg/kg) and two control materials -- Ni(II) acetate (35 mg/kg) and Ni powder 50 mg/rat).

It was observed that fibrosarcomas at the site developed as follows:

a) Ni powder - 4 to 6 months with 66% tumor incidence.

b) Nickelocene - 10 to 12 months with 36% tumor incidence

c) Ni(II) acetate - 10 to 12 months with 22% tumor incidence.

d) No tumors in controls receiving trioctanoin alone.

e) Tumors induced by nickelocene and Ni powder were 100% transferable.

The authors concluded that under the given experimental conditions, the forms of Ni tested were carcinogenic.

16. In 1969, Friedmann and Bird (206) studied the fine structure of malignant mesenchymatous tumors induced by the local injection of Ni. A single injection of Ni_3S_2 or Ni sponge was given into the right gastrocnemius muscle of 55 females Sprague-Dawley rats (200 to 250 g, wt.). Details of the tumors developed are given in Table 76.

Table 76 .

Details of Seventeen Rhabdomyosarcomas in Female Sprague-Dawley Rats (206)

Tumour no.	Animal no.	Injected material	Induction period (days)	Type of rhabdomyoblast	Histological type	Comment
1	RH 1/12	Ni_3S_2	205	III	II	
2	RH 1/16	Ni_3S_2	157	III	III	
3	RH 2/1	Ni_3S_2	174	III	II	Secondaries in regional lymph-glands
4	RH 2/2	Ni_3S_2	229	III	III	
5	RH 2/10	Ni_3S_2	195	III	III	
6	RH 2/12	Ni sponge	223	I	I	Embryonal sarcoma
7	RH 7/3	Ni_3S_2	157	III	III	
8	RH 16/1	Ni sponge	150	III	III	Necrotic
9	RH 17/1	Ni_3S_2	160	II	II	Necrotic
10	RH 17/2	Ni_3S_2	182	III	III	
11	RH 17/3	Ni_3S_2	182	II	I	Non-striated embryonal rhabdomyosarcoma
12	RH 18/1	Ni sponge	125	III	III	
13	RH 28/3	Ni sponge	240	III	III	
14	RH 30/1	Ni_3S_2	190	III	III	Multiple secondaries
15	RH 32/1	Ni_3S_2	224	III	III	
16	RH 35/1	Ni sponge	224	III	III	
17	RH 35/2	Ni sponge	238	III	III	

The observations were:

a) Out of the 55 treated rats, 17 developed primary neoplasms: 11 out of 30 injected with Ni_3S_2 and 6 out of 25 injected with Ni sponge.

b) Average latent period was ca. 190 days with a range of 125 to 240 days.

c) Most of the tumors were striated embryonal rhabdomyosarcomas.

d) Four types of rhabdomyoblasts were distinguished by electron microscopy based on the presence or absence of actin and myosin filaments, their distribution and ultimate organization into sarcomers and myofibrils.

e) An unusual structure or organelle was described; the fenestrated sarcoplasmic reticulum.

f) A comparative resistance to the oncogenic activity of Ni in Sprague-Dawley rats was noted.

17. In 1972, Lau et al. (415) investigated whether i.v. administration of liquid $Ni(CO)_4$ to rats resulted in increased malignant tumors. The experimental animals, albino Sprague-Dawley rats (eight to nine weeks old) were injected i.v. with liquid $Ni(CO)_4$. Controls received NaCl solution. The dosages and results are given in Table 77.

The authors concluded that a significant increase in the incidence of malignant tumors ($P < 0.05$) was observed in rats given six i.v. injections of $Ni(CO)_4$ in LD_{50} dosage (0.9 mg/100 g).

Table 77 .

Incidence of Malignant Tumors in Rats After i.v. Nickel Carbonyl (415)

Sprague-Dawley rats in Group A survived 1 i.v. injection of $Ni(CO)_4$ at LD_{5_0} dosage (2.2 mg nickel per 100 g). Rats in Group B survived 6 i.v. injections of $Ni(CO)_4$ at LD_5 dosage (0.9 mg nickel per 100 g) at intervals of 2 or 4 weeks. Rats in the control group received sham injections of 5 µl of 0.9% (w/v) NaCl solution.

Experimental group	No. of rats in group	Median age at death	Total incidence of malignant tumors		Pulmonary lymphomas		All other malignant tumors	
			No.	%	No.	%	No.	%
A								
	26 (M)	22 (9–25)[a]	3	11.5	2	7.7	1[b]	3.8
	46 (F)	23 (6–37)	3	6.5	2	4.3	1[c]	2.2
	72 (M, F)	23 (6–37)	6	8.3	4	5.6	2	2.8
B								
	61 (M)	21 (5–30)	10	16.4	3	4.9	7[d]	11.5
	60 (F)	24 (8–36)	9	15.0	2	3.3	7[e]	11.7
	121 (M, F)	23 (5–36)	19	15.7[f]	5	4.1	14	11.6[g]
Control								
	15 (M)	24 (10–30)	0	0	0	0	0	0
	32 (F)	24 (6–33)	2	6.3	2	6.3	0	0
	47 (M, F)	24 (6–33)	2	4.3	2	4.3	0	0

[a] Numbers in parentheses, range.
[b] Fibrosarcoma (orbit).
[c] Cholangiocarcinoma (liver).
[d] Fibrosarcomas (orbit, pinna, neck); undifferentiated sarcoma (lung); hemangioendothelioma (s.c. tissue); undifferentiated leukemia; carcinoma (kidney).
[e] Undifferentiated sarcomas (pleura, liver, pancreas, uterus, abdominal wall); carcinomas (liver, breast).
[f] $p < 0.05$ *versus* control group (χ^2 test).
[g] $p < 0.02$ *versus* control group (χ^2 test).

E. Guinea Pigs

In 1958, Hueper (285) studied the carcinogenicity of inhaled nickel powder. The test animals were 42 guinea pigs (32 male, 10 female, inbred strain 13, about three months old), exposed six hours/day for four to five days/week for a maximum of 21 months (when all animals had died) to 15 mg powdered Ni/m^3 air.

Practically all the guinea pigs developed adenomatoid proliferations in the lungs (see Table 78). In six of the animals, the intra-alveolar and intrabronchiolar

epithelial proliferations approached in circumscribed areas, the character of microcarcinomas.

The authors' conclusions were the same as those for rats, page 72, this Section D4.

Table 78.

Grades of Adenomatoid Proliferations in Lungs of Guinea Pigs After Different Periods of Exposure to Nickel Dust (285)

Grade	Exposure, Mo.	
	1-6	7-21
	Guinea Pigs, No.	
1 & 2	7	0
3 & 4	1	20

F. Rabbits

In 1955, Hueper (284) continued his investigations of the carcinogenicity of metallic Ni. To mitigate any possible effects of species - specific factors, animals other than rats, such as rabbits were also administered Ni by various routes.

Ni was administered by two routes:

a) A suspension of about 0.25 cc of powdered Ni in lanolin 12.5% Ni by volume, 43.8% by weight) was injected into the right femoral cavity of six 3-month old Dutch rabbits (1,750 to 2,000 g). A second injection of double the original amount was given 27 months later. Two controls received lanolin only. The survivals are shown in Table 79. One rabbit, surviving 43 months, developed a metastasizing endosteal fibrosarcoma of the femur.

Table 79 .

Survival Periods of Rabbits Injected Intrafemorally With Nickel (CAC) (284)

Months	13-18	31-36	37-42	43-48
Deaths	1	1	3	1

b) A suspension of 1% powdered Ni in 25% gelatin solution was given i.v. to 10 three-month old albino rabbits (2,000 to 3,000 g) six times at weekly intervals. Five controls were given similar amounts of the gelatin solution only. The survivals are shown in Table 38 , page 48 , this section. No tumors were found in these rabbits.

The author concluded that rabbits are apparently susceptible to the carcinogenic action of Ni and that the failure to show effects in rabbits injected i.v. with Ni may be explained by the fact that they did not survive long enough for the 2 to 5 year latent period for metal cancer in rabbits. (See page 71, this Section D3 for a similar experiment with rats.)

G. Humans

1. In 1958, Doll (160) statistically evaluated the risk of developing cancer of the lung and nose by Ni workers. He concluded that in the years investigated, 1948 - 1956, the risk of nickel workers dying from lung cancer was approximately five times "normal". The risk of these workers dying from cancer of the nose in these same years was approximately 150 times "normal".

Doll's findings were confirmed in another statistical investigation reported in the same year by Morgan (512) who analyzed the incidence of respiratory tract cancer in Ni workers in a nickel plant in South Wales. The frequencies of both cancer types had reverted to normal from the year 1925 when precautions against dust were installed. The author concluded that the carcinogen was in the dust and possibly was associated with arsenic.

2. In 1961, Sunderman and Sunderman (730) suggested that Ni in tobacco smoke was a potential human carcinogen. They based their recommendation that attempts should be made to remove Ni from tobacco smoke on the following evidence:

a) The authors' studies (abstracted in this section) found that the inhalation of minute amounts of Ni is carcinogenic for rats (see Table 80), a species in which spontaneous neoplasms only rarely occur.

b) In a burning cigarette, all the reactants and reaction conditions are present which are known to lead to the formation of nickel carbonyl; Ni itself (see Table 81), from 2 to 7% carbon monoxide, a temperature, 45 to 50°C, in the range at which maximum concentrations are obtained at normal pressure.

Table 80

Carcinogenic Dosages of Inhaled Nickel Carbonyl for Rats* (730)

	Inhaled $Ni(CO)_4$	Inhaled Ni
	μg.	μg.
Survivors from single heavy exposure (250 μg. $Ni(CO)_4$ per liter for 30 min.)	300	115
One year—chronic exposure† (30 μg. $Ni(CO)_4$ per liter for 30 min.; 3 times weekly)	6700	1930

* Ventillation-minute volume for rat = 0.040 l.; 30-min. volume = 1.2 l.

† $Ni(CO)_4$ inhaled per exposure = 36 μg.

Table 81

Nickel in Six (6) Brands of Cigarettes(730)

Ni (μg.) per Cigarette					
A	B	C	D	E	F (Filter)
1.59	1.75	1.85	2.30	2.48	3.07
Mean = 1.99					

c) The comparison (see Table 82) between the amount of Ni inhaled by rats which developed lung cancer and people smoking two packs/day year, shows that the exposure for people would be three times that shown to develop lung cancer in rats.

Table 82.

Comparisons of Nickel Inhalations (730)

	Nickel Inhaled	
	μg.	μg.
Carcinogenic dose for rats: 1 year of chronic exposure (30 min.; 3 times weekly)	12.4 (per exposure)	1930 (per year)
Main-stream cigarette smoke (2 packs per day)	14.8 (per day)	5400 (per year)

d) Other studies by the authors have shown that rats surviving an acute exposure of 115 µg inhaled Ni developed pulmonary cancer. The calculated amount of Ni inhaled by heavy smokers is about 47 times this value.

3. In 1962, Aspegren and Rorsman (021) investigated the occurrence of mitoses in leucocytes from normal (10 females and 5 males, 17 to 72 years old) and nickel-hypersensitive subjects (15 female, 23 to 57 years old) in short-term cultures in the presence of 1, 0.3, 0.1, 0.01 and 0.001 m M Ni in the cultures.

It was found that:

a) At a Ni concentration of 1 m M, no leucocytes from either type of subject underwent mitoses.

b) When the Ni concentration was 0.1 m M, mitoses occurred regularly.

c) Inflammation at the injection site was induced in 4 out of 12 Ni hypersensitive subjects when 0.1 m M Ni was intracutaneously injected.

d) Ni ions in vitro influenced the mitotic capacity of leucocytes from normal and nickel-hypersensitive subjects to the same degree.

4. In 1963, D'Alonzo et al. (144) reviewed the literature concerning the roles of metals in acute myocardial infarction. They found that when a group of myocardial infarction cases was compared to controls, nickel was the metal which showed the most significant elevation in the blood serum (see Table 83).

5. In 1966, Fregert and Rorsman (200) investigated the occurrence of isolated or combined allergy to three metals including Ni. The authors pointed out the importance of metal allergy from the fact that as many as 10% of 5,416 patients tested (3,087 females and 2,329 males) were sensitive to one or more of the three tested metals, Ni, Cr and Co.

Two types of tests were performed;(a patch test using 5.25% $NiSO_4 \cdot 6H_2O$ in water and an intracutaneous test using four concentrations of $NiCl_2$ (10^{-3} to 10^{-6} M).

It was found that:

a) Allergy to Ni was more common in females.

b) Ni in stainless steel is much less allergenic than in plated articles.

Table 83.

Nickel Levels in Serum of Heart Disease Patients and Matched Controls (144)

Nickel (ppm)	All Heart Disease	Controls	Coronary Insufficiency	Controls	Possible Myocardial Infarction	Controls	Definite Myocardial Infarction	Controls
ND<1	2	20	2	2	0	2	0	16
ND<2	2	0	0	0	1	0	1	0
0.5-2	2	1	0	0	0	0	2	1
1-5	8	2	0	0	0	1	8	1
2-10	11	1	0	0	2	0	9	1
3-15	0	1	0	0	0	0	0	1
Total	25	25	2	2	3	3	20	20

The authors explained their observation of allergy to more than one of the metals studied by noting the co-occurrence of various metals in sensitizing products. They considered the difference in sex distribution of allergy to one or more of the metals to be due to differences in exposure to sensitizing contacts.

BIOCHEMICAL ASPECTS

I. Breakdown

In a toxicity test in which Grandy, et al. (227) dosed mallard ducks with Ni shot, they found that at the end of the study (30 days), 4 of 15 birds retained 4 to 7 shot (average 5.7) in almost perfect condition. It was concluded that the Ni shot not retained had been passed rather than eroded or dissolved.

Perry and Perry [referenced in Schroeder, et al. (673)] found that ten daily i.v. injections of ethylene diaminetetraacetate (EDTA) did not change Ni excretion From this evidence Schroeder et al. (673) concluded that Ni in human tissues is probably chelated quite strongly since EDTA, a chelating agent, has a stronger affinity for Ni than for any other metal of the first transition group.

In 1971, Lich (433), in a review of Ni as a trace element, noted that when nickel salts are ingested they combine, for the most part, with food proteins to form insoluble compounds excreted in the feces. When in excess, or in the absence of food when the milieu is hyperacidic, they pass into the bloodstream (Royer, reference in original article).

II. Absorption and Distribution

A. Mice, Rats and Rabbits

In 1960, Selivanova et al. (684) studied spectroscopically the distribution of Ni in the organs and tissues of mice, rats and rabbits. Rats and rabbits were injected i.v. with various doses of finely dispersed metallic Ni. The purpose of this study was to determine whether previously observed lesions in the lungs following the i.v. injection of soluble Ni compounds were caused by intense irritation resulting from Ni accumulation. The results, summarized in Table 84, confirmed the correctness of the authors' assumption. Nickel content was found to be highest in the lungs during the first five days following injection and constituted about 15 to 20% of the amount of injected Ni (average weight of rats' lungs, 1.5 g; average weight of rabbits' lungs, 20 g). On the sixth and seventh days, the lungs' Ni content decreased 5 to 6-fold, which did not occur in other organs. The lungs remained, however, the richest in Ni.

In an experiment with rabbits in which soluble Ni salts (sulfate, nitrate, carbonate) were injected, Ni was found first in the kidney, liver, lung and spleen but by the sixth day, it was redistributed from other organs to the lungs, implying an affinity of Ni for lung tissue. Further evidence for the preferential uptake of

Table 84

Nickel Content of Organs in Milligrams per 100 g of Tissue Following Intravenous Injection of Finely Dispersed Metallic Nickel (684)

Survival time of animals after poisoning (in days)	Total dose used (in mg/kg)	Lungs	Kidneys	Liver	Spleen	Heart	Brain	Small Intestine	Large Intestine	Muscles	Stomach	Bone
					Rats							
3	600	730	6	4.2	1.2	2.6	0.6	0.6	0.6	0.6	0.9	0.6
5	600	690	6	4.8	1.5	1.2	0.3	0.3	0.6	0.3	0.3	0.3
5	600	438	10.2	2.7	3.3	2.04	2.4	0.3	0.3	0.3	0.6	0.3
5	600	1000	4.8	3.6	9.6	8.4	6	1.8	0.6	0.6	3.0	0.6
5	600	500	3.9	2.1	2.4	4.0	6	1.8	0.6	0.6	3.0	0.6
5	600	510	8.1	7.2	1.2	1.8	0.9	0.3	0.3	0.6	1.2	0.6
5	500	420	4.5	5.4	4.8	3.6	0.6	0.6	0.6	0.6	0.6	0.6
5	300	281	2.79	2.8	0.6	0.3	3.3	0.3	0.3	0.6	1.2	0.3
5	300	249	4.5	1.5	0.6	2.49	0.6	0.6	0.6	0.6	0.8	0.6
6	300	81	4.8	2.4	4.4	0.6	0.6	0.9	0.6	0.6	0.6	0.6
6	600	156	11.4	3.6	5.7	2.7	0.6	0.6	0.6	0.6	0.9	0.6
7	600	161	5.1	1.5	0.9	0.9	0.6	0.6	0.9	0.9	1.5	0.9
7	500	110	1.8	1.74	0.6	3.9	0.6	0.6	1.2	0.3	1.2	0.3
8	600	27.9	1.2	4.2	0.6	0.3	0.3	0.6	0.6	0.6	0.6	0.6
12	600	15.6	0.9	0.9	0.9	0.6	0.6	0.6	0.6	0.6	1.2	0.6
15	400		Not	found								
25	500		Not	found								
					Rabbits							
2	250	243	27	4.5	0.9	1.62	0.9	0.9	0.9	0.9	0.9	0.9
5	150	156	6.6	4.5	2.7	1.8	0.6	0.9	1.5	0.6	1.5	0.6
5	50	19.8	Traces	Traces	Traces	Traces	Traces	Traces	0.8	Traces	Traces	Traces
22	50	1.5	Traces	Traces	Traces	Traces	Traces	Traces	0.8	Traces	Traces	Traces

Ni by the lungs was that in controls, Ni could not be detected in any organ but the lungs where it constituted about 0.016 mg/100 g tissue.

To determine the effect on absorption of route of entry, 50 to 1200 mg finely dispersed Ni was administered p.o. to 70 white mice and 50 rats. The results are summarized in Table 85. The distribution of metallic Ni via p.o. administration differed from that observed after i.v. administration (see above and Table 84). During the first three days after administration, about 0.5% of the administered Ni was found in the kidneys, liver, lungs, spleen and heart. On the sixth day, there was a redistribution of the Ni accompanied by an increase in the amounts present in the various tissues with the lung having the highest amount. The authors suggested that the p.o. administered metallic Ni partly dissolved in the g.i. tract and was absorbed as soluble salts.

The authors concluded that their studies indicated that Ni has an affinity for lung tissue.

B. Mice

1. In 1934, Bertrand and Nakamura (058) fed weanling mice (15 experimental and 14 controls) a purified dietary mixture containing small amounts of added Ni (0.0025 g/kg Ni as Ni chloride) and Co (0.001 g/kg Co as cobalt sulfate). They found after emptying the digestive system and analyzing, the following with respect to the nickel:

In Mice Fed	Ni per	
	Mouse mg	Kg-dry mg
Without Metals	0.0004	0.047
With Ni and Co	0.0027	0.198

The authors concluded that the mice fed the diet with added Ni had retained a small but fixed part of the added metal in their tissues.

2. In 1954, Wase et al. (840) studied the metabolism of Ni^{2+} using the isotope, ^{63}Ni.

One i.p. injection of one microcurie $^{63}NiCl_2$ (102 µg) dissolved in physiological saline was given to 56 adult male mice (C57 Bl/6, 16.4 ± 1.8 g). At 2, 4, 8, 12, 24, 48 and 72 hours post injection, samples of eight mice each were sacrificed.

The results are summarized in Table 86. The observations were:

a) Maximal uptake of $^{63}Ni^{2+}$ by all tissues was achieved in 2 to 12 hours.

Table 85

Nickel Content of Organs in Milligrams per 100 g of Tissue in Rats Following Peroral Administration at a Dose of 750 mg/kg (840)

Survival time after poisoning (in days)	Lungs	Kidneys	Liver	Spleen	Heart	Brain	Muscles	Bones
1	0.08	0.75	0.1	0.158	Traces	Traces	Traces	Traces
1	0.089	0.83	0.115	Traces	Traces	Traces	Traces	Traces
3	2.4	6.3	4.2	2.3	Traces	Traces	Traces	Traces
3	1.46	3.1	1.42	0.85	Traces	Traces	Traces	Traces
6	3.2	1.27	Traces	Traces	Traces	Traces	Traces	Traces
6	0.34	0.244	0.12	0.085	Traces	Traces	Traces	Traces
11	0.16	Traces	Traces	0.05	Traces	Traces	Traces	Traces
11	0.21	0.186	0.12	0.125	Traces	Traces	Traces	Traces

Table 86 .

Distribution of Nickel in the Tissues of the Mouse Following the Administration of 1 μc $Ni^{63}Cl_2$ (102 μg Ni) (840)

Counts per minute per gram tissue

Time	Lung	Kidney	Plasma	Red blood cells	Gastro-intestinal tract	Liver	Bladder	Brain	Heart	Spleen	Carcass residue*
hr.			*per ml.*								
2	39,445	75,007	11,283	5464	3801	6,264	2856	656	2206	4733	120
4	40,247	59,504	16,466	6358	1723	9,279	2800	821	4057	4353	294
8	19,130	70,438	5,601	7281	1798	10,430	1673	868	8124	1247	210
12	18,413	53,405	2,637	6104	3402	10,172	1269	1442	2275	3221	875
24	15,687	31,262	3,048	1687	1931	4,398	1330	428	1311	—	482
48	15,210	10,253	163	339	780	873	5287	208	626	435	506
72	15,568	5,608	62	192	—	704	3602	241	516	207	70

* Carcass residue includes muscle and bone after viscera and brain have been removed.

b) The highest concentration of Ni was found in kidney, lung and plasma; the least in brain and muscle.

c) Except for the lungs and brain, Ni disappeared rapidly from all tissues.

d) After 72 hours, the lungs retained, 38.6% and the brain, 16.7%.

e) After 72 hours, the ratios of the concentration of tissue Ni to serum Ni were: lungs, 250.6; kidney, 90.5; liver, 11.3; heart, 8.3; brain, 3.88; spleen, 3.34; erythrocytes, 3.08; and carcass, 1.13.

The authors concluded that their experimental data indicated Ni^{2+} to be widely distributed and rapidly eliminated from the organism. They postulated that the relatively high Ni retention by pulmonary tissue suggested a high value for the complex-formation constant of Ni^{2+} and lung protein.

3. In 1963, Schroeder et al. (676) found that mice given 5 ppm Ni (as the acetate) in drinking water for their lifetimes showed a considerable increase in Ni concentration in their tissues as compared to controls. The following data compares the Ni in an organ of high concentration — the kidney, for mice dying at 360 to 480 days of age and for man. (See page 57, Biological Data III A2, for experimental details.)

Mice		Adult Man	
Control	Given Ni.	Mean	Range
µg/g wet wt.	µg/g wet wt.	µg/g wet wt.	µg/g wet wt.
0.08 - 0.59	0.9 - 3.7	0.9	<0.05 - 0.9

4. In 1964, Schroeder et al. (674) found moderate increases of Ni in five organs as compared with controls in mice given 5 ppm Ni in drinking water for their lifetime (for experimental details, see page 60, Biological Data III A3). The mean concentration of Ni in five organs according to sex, of mice 100 to 800 days or more or age is compared with literature values for adult man in Table 87. The levels in the organs of highest concentrations according to three ages are shown in Table 88.

Table 87.

Organ Concentrations of Nickel in Mice and Man[1] (674)

	No.	Kidney	Liver	Heart	Lung	Spleen	Mean[2]	Metal in food and water[3]
		µg/g wet wt	µg/g wet wt	µg/g wet wt	µg/g wet wt	µg/g wet wt		ppm
Mice								5.4
Males	33	0.93	0.78	1.05	1.13	2.76	1.33	
Females	27	1.07	0.75	0.72	0.53	4.16	1.45	
% present		71	78	75	70	91		
Control mice[5]								0.4
Males	69	0.52	0.62	0.43	0.32	0.42	0.46	
Females	30	0.46	0.20	0.0	0.61	0.33	0.32	
% present		100	87	67	67	75		
Adult man	145	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	< 0.14	0.2
% present		21	18	34	50	12		

[1] The levels for adult man are the means obtained by spectrographic methods from Tipton and Cook (10), subjects from the U.S. Mainland, and show general levels in tissues. The ranges in all cases were wide.
[2] The means of the averages for each organ are shown as indexes of relative tissue concentrations and are not to be construed as representing other than aids to the reader in comparing treated with control groups.
[3] Food and water values are measured levels for mice and approximations based on analyses for man (5-9).
[4] Percentage of organs analyzed in which the designated metal was detected.
[5] Controls represent all animals not given the metal indicated.
[6] No metal detected by analysis.

Nickel tended to accumulate in the spleen and heart. In male mice, the Ni concentrations in kidney (0.0 to 3.7 µg/g) and liver (0.0 to 2.5 µg/g) decreased almost regularly from 300 to 755 days of age. In females this decrease occurred only in the liver (0.0 to 2.3 µg/g).

Table 88

Ni in Tissues of Mice in Relation to Age, Both Sexes; Organs of Highest Mean Concentrations[1] (674)

Organ	100 - 300 Days	360 - 560 Days	560 - 800 Days
Heart	1.02	0.69	1.77
Kidney	1.85	0.78	0.57
Spleen	3.60	1.27	3.57

[1] 5 ppm metal were given in drinking water continuously.

The author concluded with the observations that in humans nickel is commonly found only in the skin. The level in mice, whether or not fed Ni, was higher, though within human ranges.

C. Rats

1. In 1950, Phatak and Patwardhan (591) studied the distribution of Ni in the tissues of rats fed diets for eight weeks supplemented with 25, 50 and 100 mg/100 g basal diet of Ni from three sources: Ni carbonate, Ni soaps of mixed acids of refined arachis oil, and Ni catalyst suspended in oil. Rats on all the Ni-containing diets were found to retain an appreciable quantity of Ni (see Table III, in Biochemistry III on page 114). Retention on the Ni carbonate diet was the highest.

The distribution of Ni in various tissues (except lung) is summarized in Table 89. When arranged in order of decreasing Ni content, it is bone, spleen, kidney heart, intestine, blood and testes. Tissues of rats on Ni-carbonate had a higher Ni content than the other two groups at corresponding levels of Ni intake.

To ascertain whether Ni retained in the mother's body could be transferred to offspring, rats from the eight-week feeding study were mated and continued on the Ni containing diets through gestation and lactation (three to four or more months). The amount of Ni found in the whole body of newborns is shown in Table 25, Biology II (page 35). The animals born of mothers fed Ni carbonate showed the highest Ni content. Those from mothers in all three groups, on the lowest Ni supplement, 25 mg/100 g diet, had no Ni in their bodies. (Contrary data for calves was reported by O'Dell et al., page 110, this Section F.)

Table 89

Distribution of Nickel in Tissue (591)

All the figures are for 100 gm. of fresh tissue weight

Group No. & mg. of Ni/100 gm. diet	Bones mg.	Liver mg.	Kidney mg.	Spleen mg.	Heart mg.	Intestine mg.	Testes mg.	Blood mg.	Skin mg.
Nickel Carbonate									
I — 100	35·85 34·69	1·11 1·30	4·31 3·37	2·86 3·31	5·01 4·00	2·54 2·56	1·86 2·68	3·10 2·11	1·25 0·71
II — 50	28·89 22·88	1·32 0·43	1·15 3·06	2·82 3·36	2·03 1·24	2·18 1·50	5·89 0·59	1·01 1·30	0·84 0·36
III — 25	18·76 13·52	0·10 0·15	1·19 1·00	0·55 0·28	0·79 0·76	1·84 0·69	1·32 2·33	0·45 0·34	0·24 0·10
Nickel Soaps									
I — 100	25·30 21·82	1·31 1·15	3·48 2·98	4·84 3·22	1·69 2·50	1·05 1·40	1·80 nil	1·08 1·17	0·78 0·78
II — 50	8·22 8·45	0·98 1·15	2·39 2·71	1·47 2·48	1·73 2·90	1·19 1·18	0·71 0·36	0·84 1·21	0·57 0·53
III — 25	3·60 5·33	0·42 0·57	1·44 2·02	0·92 1·65	0·85 0·91	0·64 0·74	nil nil	0·21 0·54	0·11 0·43
Nickel Catalyst									
IV — 100	14·73 17·56	0·89 1·27	2·55 2·37	3·47 1·85	1·79 2·29	1·05 1·28	0·22 0·55	0·84 1·00	0·58 0·65
V — 50	7·97 9·42	0·64 0·87	1·00 1·52	1·31 0·99	1·44 1·67	0·74 0·83	0·33 0·79	0·39 0·48	0·37 0·27
VI — 25	3·60 3·09	0·48 0·37	1·09 0·58	nil nil	1·03 0·63	0·51 0·84	0·92 nil	0·45 0·48	0·23 0·31
Control	nil nil	nil nil	nil nil	nil nil	nil nil	nil nil	nil nil	nil nil	nil nil

2. In 1952, Phatak and Patwardhan (592) studied the accumulation of Ni in rats' tissues with continuous feeding of 25 mg Ni/100 g diet over a period of 16 months. Four rats were sacrificed at 4, 8, 12 and 16 months for determination of tissue Ni content. The data are summarized in Table 90.

Table 90

Distribution of Nickel in Tissues (592)

(All the figures are based on 100 g of fresh tissues)

Duration of Feeding, Months	No. of Animals	Bone, mg	Liver, mg.	Kidney, mg.	Spleen, mg.	Heart, mg.	Intestine, mg.	Testes, mg.	Blood, mg.	Skin, mg.
4	4	7·50	0·28	0·55	2·70	2·10	0·61	0·43	0·76	0·07
8	4	8·40	0·36	2·82	5·36	2·37	0·71	1·10	0·91	0·09
12	4	8·63	0·17	2·00	2·77	3·00	0·52	0·64	0·50	-
16	4	7·30	0·13	2·30	1·90	2·00	0·46	0·52	0·45	-

Previous research by the authors (reference in original paper) had found that when Ni contents at the end of four months on a Ni-containing diet was compared with two months, there was an increase in the Ni content of bone, spleen, heart, intestine

and blood, and a decrease in liver, kidney and skin. The tissue accumulation of Ni continued up to eight months when it reached a maximum, falling thereafter despite continuation of dietary Ni.

The data from this experiment, summarized in Table 90, show that with prolonged feeding (16 months) the tissue accumulation of Ni is not progressive and reaches a plateau. (Note: Lung was not examined in the studies by these authors.)

A second experiment was carried out to investigate whether a low protein diet, approximating the diet of poor people in India, would affect Ni accumulation in the tissues. (The nutrient contents of the diets are shown in Table 91.)

Table 91 .

Nutrient Content of Experimental Diets (592)

(*Figures relate to* 100 *g. of diet.*)

	Basal	Low protein
Fat, g.	11·4	11·1
Protein, g.	16·4	6·8
Calcium, mg.	754·0	750·0
Phosphorus, mg.	660·0	680·0
Iron, mg.	20·0	19·0

One of two groups of young rats (four to five weeks, 12 rats/group) was fed a low protein diet with added 25 mg Ni/100 g diet (as Ni catalyst). The other group was fed the same diet used in the previous experiments.

The results are summarized in Table 92. They show that there was no increased Ni accumulation on the low protein diet. There seemed rather to be a tendency to lower accumulation of Ni in the tissues. The authors concluded that on a low protein (6.8%) diet, the accumulation of Ni was less in all the tissues (with the exception of the intestine) than when the dietary protein was normal (16.4%).

Table 92.

Distribution of Nickel in Tissues on Low and Normal Protein Diets (592)

(*No. of animals killed,* 4; *all figures based on* 100 *g. of fresh tissues*)

Diet	Duration of feeding, months	mg. nickel in								
		Bones	Liver	Kidney	Spleen	Heart	Intestine	Testes	Blood	Skin
Low protein	4	4·15	0·28	0·43	1·66	0·62	0·92	0·28	0·57	—
Normal	4	6·50	0·31	0·69	2·65	2·13	0·57	0·66	0·59	0·01
Low	8	6·40	0·24	1·68	2·00	1·00	0·58	0·66	0·58	0·02
Normal	8	7·93	0·41	2·20	4·23	2·35	0·61	0·86	0·81	0·04

3. In 1957, Sunderman et al. (735) showed that when rats are subjected to both acute and chronic exposure to $Ni(CO)_4$, the concentrations of Ni in these organs are increased. (See data in Table 93 and for experimental details, see page 62, Biological Data III B2.) A summary of the changes in organ weights of the rats subjected to chronic exposure is give in Table 94. The total Ni contents in the liver and kidney increased, as is shown by the observation that there was little change in their mean weights.

Table 93- Nickel in Tissues of Animals After Exposure to $Ni(CO)_4$ (735)

Group	Ni, µg. Gm. of Wet Tissue	
	Mean Liver Value	Mean Kidney Value
Control	0.12 (SE ± 0.02)	0.40 (SE ± 0.13)
Chronic*	0.20 (SE ± 0.05)	1.21 (SE ± 0.05)
Acute L.D. exposure†	0.48 (SE ± 0.29)	0.95 (SE ± 0.13)

*These analyses were made on tissues from animals killed 6 to 12 months after the start of the program.

†These analyses were made on tissues obtained 48 to 168 hours after exposure.

4. In 1962, Schroeder et al. (673) suggested that there appeared to be a mechanism in mammals limiting intestinal absorption similar to that for iron, manganese and copper. They cited as evidence, the research of Phatak and Patwardhan (591 and 592, page 99 and 100, this Section C1 and 2) in which it was shown that large Ni doses were required to overcome this mechanism. When rats were fed large amounts (250 to 1000 ppm) of Ni (as carbonate) for two months, the major portion of the Ni was accumulated by bone (135 to 358 ppm) with 10 to 50 ppm found in the other tissues.

Table 94 - Per Cent of Total Body Weight of Various Organs of Rats Subjected to Chronic Exposure of Nickel Carbonyl (735)

Group		Organ Weight as Per Cent of Total Body Weight. Per Cent ± S. E.	Per Cent Increase
C	Liver	2.97 ± 0.11	
X		3.07 ± 0.15	
Z		2.95 ± 0.19	
C	Lung	0.69 ± 0.17	
X		2.20 ± 0.18	219
Z		1.69 ± 0.22	145
C	Heart	0.33 ± 0.04	
X		0.53 ± 0.03	61
Z		0.52 ± 0.13	60
C	Kidney	0.36 ± 0.04	
X		0.40 ± 0.02	
Z		0.43 ± 0.03	
C	Adrenal	0.0057 ± 0.0006	
X		0.0119 ± 0.0012	109
Z		0.0124 ± 0.0009	118

C = control.
X = 0.03 mg per liter for 30 minutes, three times weekly for one year.
Z = 0.06 mg per liter for 30 minutes, three times weekly for one year.

5. In 1968, Smith and Hackley (705) studied the distribution of ^{63}Ni administered i.v. in trace amounts (0.74 µg or 1.47 µg ^{63}Ni as $^{63}NiCl_2$ in 1 N HCl and normal saline) to female Sprague-Dawley rats (218 to 26 g).

In the first experiment, five animals per group were injected i.v. with 2.5 µCi ^{63}Ni (0.74 µg) and killed at intervals. In the second experiment, four animals per group were similarly injected with 5.0 µCi ^{63}Ni (1.47 µg) and similarly sacrificed at intervals. The results are summarized in Tables 95 and 96.

Table 95.

Distribution of ^{63}Ni in Selected Tissues at Timed Intervals After Single Intravenous Dose[1] (705)

Time after dose	Kidney	Lung	Spleen	Liver	Femur
hours			*% dose/g fresh tissue*		
0.25	6.54 ± 0.50	0.97 ± 0.06	0.40 ± 0.30	0.36 ± 0.03	0.24 ± 0.02
1	5.47 ± 0.38	0.66 ± 0.03	0.22 ± 0.01	0.24 ± 0.01	0.16 ± 0.01
2	4.46 ± 0.36	0.42 ± 0.03	0.14 ± 0.01	0.14 ± 0.01	0.08 ± 0.01
4	2.36 ± 0.16	0.32 ± 0.01	0.10 ± 0.00	0.12 ± 0.01	0.04 ± 0.00
8	1.57 ± 0.16	0.18 ± 0.01	0.05 ± 0.00	0.06 ± 0.01	0.01 ± 0.00
16	0.95 ± 0.06	0.11 ± 0.01	0.03 ± 0.00	0.03 ± 0.00	nd [2]
24	0.92 ± 0.11 [3]	0.11 ± 0.01 [3]	0.07 ± 0.01 [3]	0.02 ± 0.00 [3]	nd [3]
48	0.52 ± 0.04	0.03 ± 0.00	0.01 ± 0.00	nd	0.01 ± 0.00
72	0.27 ± 0.02	0.02 ± 0.00	0.01 ± 0.00	nd	0.01 ± 0.00

[1] Mean ± SE, 5 animals/group.
[2] Non-detectable.
[3] Four animals used for 24-hour interval.

Table 96.

Distribution of ^{63}Ni in Selected Tissues at Time-Intervals After Single Intravenous Dose[1] (705)

	Hours after dose				
	0.25	2	6	16	72
			% dose/g fresh tissue		
Kidney	2.49 ± 0.54	2.57 ± 1.24	0.59 ± 0.23	0.20 ± 0.06	0.11 ± 0.06
Adrenal	0.92 ± 0.14	0.28 ± 0.03	0.15 ± 0.01	0.12 ± 0.02	0.03 ± 0.01
Ovary	0.90 ± 0.33	0.23 ± 0.06	0.11 ± 0.02	0.09 ± 0.01	nd [2]
Lung	0.81 ± 0.04	0.29 ± 0.04	0.14 ± 0.03	0.09 ± 0.01	0.01 ± 0.00
Heart	0.64 ± 0.04	0.21 ± 0.02	0.11 ± 0.01	0.07 ± 0.01	nd
Eye	0.56 ± 0.06	0.19 ± 0.03	0.13 ± 0.04	0.08 ± 0.03	0.01 ± 0.00
Thymus	0.55 ± 0.03	0.15 ± 0.02	0.12 ± 0.02	0.04 ± 0.01	nd
Pancreas	0.54 ± 0.05	0.16 ± 0.03	0.12 ± 0.03	0.08 ± 0.01	nd
Spleen	0.48 ± 0.03	0.13 ± 0.01	0.11 ± 0.01	0.09 ± 0.01	0.01 ± 0.00
Liver	0.40 ± 0.03	0.13 ± 0.02	0.08 ± 0.01	0.05 ± 0.01	nd
Skin	0.38 ± 0.08	0.20 ± 0.05	0.07 ± 0.01	0.04 ± 0.01	nd
G.I. tract	0.33 ± 0.04	0.21 ± 0.04	0.11 ± 0.03	0.10 ± 0.01	nd
Muscle	0.29 ± 0.07	0.11 ± 0.05	0.04 ± 0.01	0.03 ± 0.05	nd
Teeth	0.21 ± 0.04	0.08 ± 0.02	0.04 ± 0.01	0.03 ± 0.01	0.01 ± 0.00
Femur	0.15 ± 0.02	0.05 ± 0.01	0.03 ± 0.01	0.01 ± 0.00	nd
Brain	0.15 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	0.05 ± 0.02	nd
Adipose	0.14 ± 0.04	0.04 ± 0.01	0.02 ± 0.00	0.01 ± 0.01	nd
Carcass	—	—	—	—	nd

[1] Mean ± SE, four animals/group.
[2] Non-detectable.

The observation in this experiment that all of the radioactivity of whole blood could be accounted for by the plasma fraction is in disagreement with Wase et al. (see page 95, this Section B2) who found that in mice the red blood cells contained about one-half the activity of plasma.

The authors pointed out this is the first study of normal concentration of Ni in adrenal and ovary. A relatively high activity was found in these organs. Lung had the second highest ^{63}Ni concentration of the tissues analyzed in the first experiment and the fourth highest in experiment 2.

In Table 97, the distribution of ^{63}Ni in various tissues and organs was compared to the relative blood volume. At 15 minutes, 2, 6 and 16 hours following the ^{63}Ni i.v. injection, a high correlation was found to exist between ^{63}Ni distribution and blood volume. The authors considered that their data strongly suggested that the ^{63}Ni distribution was directly related to blood volume of the specific organ or tissue studied.

Table 97 .

Comparison of ^{63}Ni Distribution with Tissue Blood Volume (705)

Tissue [1]	^{63}Ni distribution [2]				Blood vol [3]
	15 min	2 hr	6 hr	16 hr	
	% dose/g fresh tissue				*µliters/g*
Adrenal	0.92	0.28	0.15	0.12	268
Ovary	0.90	0.23	0.11	0.09	268
Lung	0.81	0.29	0.14	0.09	505
Heart	0.64	0.21	0.11	0.07	238
Spleen	0.48	0.13	0.11	0.09	134
Liver	0.40	0.13	0.08	0.05	265
Skin	0.38	0.20	0.07	0.04	18.2
Muscle	0.29	0.11	0.04	0.03	22.9
Femur	0.15	0.05	0.03	0.01	32.8
Brain	0.15	0.04	0.04	0.05	30.1
Correlation coefficient	0.79	0.76	0.82	0.68	
	$P < 0.01$	$P < 0.05$	$P < 0.01$	$P < 0.05$	

[1] Kidney was omitted due to radioactive urine within it.
[2] No comparison could be made for the 72-hour interval because ^{63}Ni was non-detectable in several tissues (see table 2).
[3] Blood volume data from Everett et al. (18).

6. In 1974, Schroeder and Nason (671) investigated what effect the trace metal Ni would have on the tissue concentrations of other trace metals in rats (Long-Evans strain) given 5 ppm Ni in drinking water for life (mean age 933 days). It was found that compared to the plain water group; zinc was increased in all organs but liver, copper was increased in spleen; manganese was increased in lung and kidney; and chromium was increased in liver and kidney. The authors concluded that in some organs their data demonstrated interactions of Ni with copper and manganese.

7. In a continuation of the previous experiment, Schroeder et al. (675) evaluated the interaction of Ni with the essential metals - zinc (Zn); copper (Cu); chromium (Cr) and manganese (Mn). Rats (Long-Evans BLU:(LE) strain, male and female) were given 5 ppm Ni in drinking water for life (104 experimental, 104 controls).

The effects of feeding Ni on the four essential trace metals in five organs of the rats are summarized in Table 98. It can be seen that compared to rats not fed Ni, there was some suppression of the levels of Zn and Cu in lung and of Mn and Cu in spleen. There was more Cr in heart and spleen and more Mn in kidney. No accumulation of Ni in tissues was observed. (For a contrary finding, see pages 99 and 100, Phatak and Patwardhan (591 and 592) this Section C1 and C2).

The authors concluded that Ni mobilized and promoted the excretion of Cu, Zn and Mn from one or two organs and promoted the storage of Cr and Mn in one or two organs. They considered this as supporting evidence for the idea that most essential trace metals interact in the body to one degree or another by unknown mechanisms.

Table 98.

Trace Metals in Tissues of Rats Fed Nickel, Dry Weight, Both Sexes Combined (675)

Organ	Control-3 μg/g	P[1]	Nickel-fed μg/g	Control-3 μg/g	P[1]	Nickel-fed μg/g
		Copper			Zinc	
No. rats/no. samples[2]	(22/7)		(63/10)	(22/6)		(64/10)
Liver	22.8 ±4.88[3]	—	20.7 ±7.09	142 ±12.8	—	94 ±20
Lung	15.2 ±1.28	<0.01	9.8 ±0.97	80 ± 5.4	<0.05	60 ± 5.7
Heart	22.7 ±5.29	—	32.8 ±7.39	117 ±11.0	—	99 ±14.0
Kidney	22.1 ±6.58	—	27.0 ±5.76	108 ± 9.2	—	128 ±19.8
Spleen	24.2 ±2.75	~0.25	16.3 ±2.24	124 ±11.7	—	100 ±10.2
α[4]		—			0.01	
Intake in food & water	6.36		6.36	72.3		72.3
		Chromium			Manganese	
No. rats/no. samples[2]	(29/8)		(64/10)	(24/10)		(63/10)
Liver	0.51±0.078	—	0.41±0.061	4.5± 1.04	—	4.0± 0.87
Lung	2.03±0.738	—	1.04±0.375	1.8± 0.33	—	1.8± 0.28
Heart	0.61±0.100	<0.025	1.86±0.406	2.7± 0.46	—	3.1± 0.73
Kidney	0.94±0.270	—	1.48±0.247	2.2± 0.52	<0.025	4.2± 0.79
Spleen	1.11±0.365	<0.05	2.97±0.679	3.2± 0.59	<0.025	1.8± 0.40
Intake in food & water	5.14		5.14	22.7		22.7

Organ	Control-3 μg/g	P[1]	Nickel-fed μg/g
		Nickel	
No. rats/no. samples[2]	(34/9)		(64/10)
Liver	1.3±0.12	—	1.2±0.20
Lung	2.4±0.53	—	2.7±0.52
Heart	3.0±0.94	—	3.2±0.39
Kidney	1.7±0.46	—	3.0±0.70
Spleen	6.2±1.83	—	4.9±0.87
Intake in food & water	0.44		5.44

[1] P is the significance of the difference between contiguous mean values, by Student's t. [2] Numbers in parentheses are total number of rats/number of pooled samples. Organs were pooled in groups of one to ten; more than half were in groups of three to five. [3] Weighted mean ± SEM according to number of rats and samples in each pool. Note: Data on the two sexes separately, as well as on both sexes combined, have been filed with the National Auxiliary Publications Service of the American Society for Information Services. There was more chromium in the livers of females and nickel than of males, and less in male lungs than control-3 ($P < 0.05$). There was more zinc in control-3 male livers than nickel-fed males ($P < 0.01$), and more nickel in plain water male livers than in nickel-fed ($P < 0.05$). A dash indicates $P > 0.05$.

D. Chicks

In 1970, Nielsen and Sauberlich (537) investigated whether Ni performs a physiological role for the chick.

Nine three-week old White Rock chicks were given 25 μCi ^{63}Ni (as $^{63}NiCl_2$) by gavage (5 μg Ni) after being on a low Ni diet for three weeks (<0.08 ppm Ni). Controls received a diet supplemented with 5 ppm $NiCl_2 \cdot 6H_2O$.

The results are summarized in Table 99. It was observed that:

a) During the six hours after dosage, bone, kidney, liver and aorta took up relatively large amounts of ^{63}Ni but very little was found in muscle, and blood (red-blood cells and plasma).

b) After 48 hours, a large amount of ^{63}Ni was still retained by bone, kidney and liver.

The authors concluded that their data supported the contention that Ni may have a physiological role in the chick (see page 46 , Biological Data II F3).

Table 99.

Distribution of ^{63}Ni in Selected Tissues at Time Intervals After a Single Dose (Experiment 2).[a] (537)

Tissue	Hours after dose: 6		24		48	
	Ni Low[b]	Ni High[c]	Ni Low	Ni High	Ni Low	Ni High
	(% dose/g fresh tissue)					
Bone[d]	0.296[d]	0.128[e]	0.101	0.076	0.099[j]	0.041[k]
Epiphyseal plate	0.102	0.070	0.023	0.024	0.015	0.017
Primary spongiosa	0.134	0.072	0.034	0.023	0.029	0.024
Hyaline cartilage	0.096	0.043	0.017	0.011	0.016	0.008
Blood	0.041	0.035	0.004	0.005	0.002	0.002
Red blood cells	0.021	0.015	0.002	0.002	0.002	0.001
Plasma	0.054	0.044	0.044	0.006	0.005	0.002
Duodenum	0.035	0.044	0.008	0.008	0.006	0.005
Kidney	0.069	0.202	0.291	0.073	0.193	0.141
Spleen	0.044[l]	0.023[m]	0.021	0.020	0.017	0.010
Liver	0.103[n]	0.042[o]	0.062	0.039	0.069	0.035
Lung	0.052	0.030	0.012	0.011	0.019	0.010
Muscle	0.018	0.017	0.003	0.004	0.003	0.003
Skin	0.051	0.048	0.019	0.022	0.023	0.023
Aorta	0.157[q]	0.053[r]	0.026	0.016	0.021	0.025
Heart muscle	0.020	0.029	0.016	0.023	0.009[s]	0.032[t]
Feather	0.032	0.035	0.040	0.049	0.064	0.046
Gizzard lining	0.102[f]	0.196[g]	0.008[h]	0.016[i]	0.006	0.005

[a] Each value represents the mean of three chicks.

[b] Ni Low indicates those chicks fed the basal diet which contained <0.08 ppm nickel on an air dried basis.

[c] Ni High indicates those chicks fed the basal diet supplemented with 5 ppm nickel.

[d,e,f,g,h,i] Significant at the 0.1 level.

[j,k,l,m,n,o,p,q,r,s,t] Significant at the 0.5 level.

E. Dogs

In 1939, Caujolle and Canal (112) studied the concentration of Ni in the viscera and tissues of dogs administered Ni i.v. (as $NiCl_2$).

The localization and concentration of Ni found in the various viscera examined for six dogs is shown in the following Tables:

Table 100 - 340 mg Ni in 200 cc physiologic serum injected;

Table 101 - 852 mg Ni in 500 cc physiologic serum injected;

Table 102 - 455 mg Ni in 500 cc physiologic serum injected;

Table 103 - 130 mg Ni in 150 cc physiologic serum injected;

Table 104 - 88.9 mg Ni (10 mg/kg) injected;

Table 105 - 345 mg Ni injected.

The authors concluded from their observations that:

a) Kidneys concentrated a higher amount of Ni, and liver a lower amount.

b) Brain did not appear to concentrate Ni; heart contained an appreciable amount; and the endocrines a small amount.

c) Their studies did not confirm those of Riche and Laborde (reference in original paper).

Table 100.

Ni Distribution in Viscera (112)

Organ	Total Wt. in g.	Total Ni in mg.	Ni in mg p. 100
Heart	116	3.5	3.0
Kidney	90	5.4	6.0
Liver	412	2.3	5.5
Tongue	70	1.9	1.3
Stomach + its contents	257	2.0	4.6
Lungs (Pieces)	(44)	Clear presence	(less than 0.5)
Pancreas	21.5	minute	traces
Spleen	38	1.4	0.5
Brain	70	minute	traces

Table 101 .

Amount of Ni (in mg.) in Carotid Blood;
1.66 (puncture done immediately before sacrifice) (112)

Organ	Total Wt. in g.	Total Ni in mg.	Ni in mg. p. 100
Heart	168	1.67	1.0
Kidney	106	5.1	4.8
Liver	738	47.2	6.4
Tongue	75	3.1	4.1
Stomach and its contents	290	15.4	5.3
Lungs (pieces)	(180)	"	2.9
Pancreas	39	1.1	2.8
Spleen	70	0.27	0.4
Suprarenals			
Brain	76	Minute	traces
Cranial bone	(76)	slight	traces
Masticatory muscles	(52)	"	0.6

Table 102.

Amount of Ni (in mg.) in Carotid Blood:
1.05 (puncture done just before sacrifice) (112)

Organ	Total Wt. in g.	Total Ni in mg.	Ni in mg. p. 100 g.
Heart	120	2.5	2.1
Kidneys	120	5.6	5.6
Liver	620	42	6.7
Pancreas	52	0.8	2.5
Spleen	50	2.0	4.0
Brain	80	Minute traces	
Muscular mass from the paw	(107)	0.51	4.8

Table 103
Ni Distribution in Viscera (112)

Organ	Total Wt. in g.	Total Ni in mg.	Ni in mg p. 100 g.
Heart	145	0.6	0.4
Kidney	73	2.6	3.5
Liver	505	(abundant)	(abundant)
Spleen	44	0.5	about 1
Brain	79	0	0
Stomach	40	0.8	2.0

Table 104.

Amount of Ni (in mg p. 100 g) of Carotid Blood:
Less Than 1 mg (puncture done immediately following death) (112)

Organ	Total Wt. in mg.	Total Ni in mg.	Ni i mg p. 100
Kidney	55	1.8	3.2
Liver	201	20.0	6.84
Stomach and its contents	250	0.96	0.35
Pancreas	38	0	0
Cranial bone	60	0	0
Small intestine and its contents	74	0.81	1.1
Cephalorhachidian fluid	12 cm^3	Slight traces	

Table 105.

Amount of Ni (in mg p. 100 g) of Carotid Blood Sampled at Death:2.51 (112)

Organ	Total Wt. in g.	Total Ni in mg	Ni in mg p. 100 g
Kidney	97	3.7	3.75
Liver	465	15.81	3.40
Brain	73	Very slight traces	
Suprarenals	not weighed	Very slight traces	
Salivary glands	not weighed	slight traces	

F. Calves

In 1971, O'Dell et al. (551) studied the tissue distribution of Ni in 12 male Holstein calves fed supplementary dietary Ni (as $NiCO_3$) at levels of 0, 62.5, 250, and 1000 ppm for five days.

The results are shown in Table 106. It was observed that:

a) Tissue Ni content did not differ statistically at the three lowest levels (0, 62.5 and 250 ppm Ni).

b) At 1000 ppm Ni there was a highly significant ($P < 0.01$) increase in Ni content of many tissues.

Table 106.

Effect of Nickelous Carbonate in the Diet on Nickel Level of Bovine Tissue (551)

Tissue	Level of nickel supplementation, ppm: 0	62.5	250	1,000	SE[a]
	μg Ni/ml				
Serum	0.61[b]	0.80[b]	0.25[b]	2.88[c]	0.29
	μg Ni/g dry matter				
Serum	0.00[b]	0.00[b]	3.19[b]	37.66[c]	4.25
Kidney	2.08[b]	1.85[b]	2.26[b]	22.43[c]	1.91
Vitreous humor	0.00[b]	0.01[b]	0.35[b]	6.42[c]	0.60
Lung	2.91[b]	2.81[b]	13.64[b]	5.85[b]	4.15
Testis	0.46[b]	0.55[b]	0.95[b]	4.78[c]	0.13
Bile	0.00[b]	0.00[b]	0.27[b]	3.84[c]	0.23
Tongue	0.55[b]	0.37[b]	0.82[b]	3.14[c]	0.17
Pancreas	0.00[b]	0.23[b]	0.41[b]	2.71[c]	0.51
Rib	0.25[b]	0.30[b]	0.00[b]	2.32[c]	0.21
Spleen	0.00[b]	0.00[b]	0.00[b]	1.85[c]	0.05
Brain	0.00[b]	0.00[b]	0.02[b]	1.33[c]	0.09
Liver	0.72[b]	0.88[b]	0.37[b]	0.53[b]	0.27
Heart	1.11[b]	0.93[b]	0.52[b]	0.50[b]	0.35

[a] Standard error of a mean, three animals per treatment.
[b-c] Mean values within a row that are not followed by the same superscript are significantly different ($P<.01$).

c) Accumulation of Ni was in the order; serum > kidney > vitreous humor > lung > testis > bile > tongue > pancreas > rib > spleen > brain.

d) At any treatment level, liver and heart concentrations were not significantly different.

The authors noted that their data differed widely from that reported by Phatak and Patwardhan for rats (591 , page 99 , this Section C1).

Data for Ni content in digestive tract tissues are shown in Table 107.

Table 107.

Effect of Dietary Nickel Levels on Ni Content of Digestive Tract Tissues (551)

Tissue	Level of nickel supplementation, ppm: 0	62.5	250	1,000	SE[a]
	μg Ni/g dry tissue				
Rumen-reticulum	0.46[b]	10.53[c]	8.62[d]	7.64[c]	0.28
Omasum	0.57[b]	4.45[c]	10.63[d]	8.58[d]	0.63
Abomasum	0.07[b]	0.43[b]	1.36[b]	6.13[c]	1.00
Duodenum	0.53[b]	0.90[b]	8.96[b]	29.12[c]	4.60
Small intestine, 1st half	0.37[b]	1.12[b]	7.15[c]	14.02[d]	1.83
Small intestine, 2nd hali	0.13[b]	0.82[c]	1.54[d]	5.83[e]	0.14

[a] SE—Standard error of a mean, three animals per treatment.
[b-e] Mean values within a row that are not followed by the same superscript are significantly different ($P<.05$).

Table 107 shows:

a) Abomasal, duodenal and intestinal Ni content increased with increasing dietary Ni levels.

b) The sites of greatest absorption in animals fed 1000 ppm Ni were in the duodenum and first half of the small intestine.

c) In both the 250 and 1000 ppm Ni-fed groups, the level of Ni declined about 80% between duodenal tissue and the second half of the small intestine.

G. Cows

In 1971, O'Dell et al. (552) determined the amount of Ni appearing in the milk of lactating cows fed Ni (as $NiCO_3$) with their diet ration added to provide 0, 50, and 250 ppm on an as-fed basis. The amount of Ni found in the milk is shown in Table 108. The authors'concluded that Ni in the cow's diet would not add appreciably to the Ni content of its milk.

Table 108.

Nickel in Milk From Cows Fed Supplemental Nickel in Concentrate (552)

Animal number	Nickel supplementation in concentrate					
	0 ppm		50 ppm		250 ppm	
	Basal[a]	Treatment[b]	Basal	Treatment	Basal	Treatment
	(ppm)					
1	0.03	0.03	0.11	0.01	0.01	0.05
2	0.07	0.00	0.19	0.01	0.02	0.01
3	0.00	0.04	0.12	0.02	0.08	0.03
4	0.15	0.03	0.09	0.02	0.00	0.00
5	0.15	0.02	0.20	0.05	0.00	0.00
Average	0.08	0.02	0.14	0.02	0.02	0.02

[a] Basal, concentrate without supplemental nickel.
[b] Treatment, concentrate with supplemental nickel.

H. Humans

In 1963, D'Alonzo and Pell (143) found that 19 out of 20 myocardial infarction (m.i.) patients had abnormally elevated Ni levels (see Table 109) in the range of 0.5 to 2 ppm or higher (normal range of Ni in plasma estimated as 0.0 to 0.27 ppm).

Table 109

Levels of Ni in Serum of Myocardial Infarction Patients and Matched Controls (143)

		Serum Levels in PPM				
		Total	ND <2	0.5-2 to 3-15	Pct. 0.5-2 to 3-15	P*
Ni	MI	20	1	19	95.0	0.0000022
	Controls	20	16	4	20.0	

* Two-tailed probability computed by Fisher's exact treatment of 2 x 2 contingency tables.

The authors presented evidence for two hypotheses for the high levels of serum Ni: as a consequence of m.i. or because Ni is involved in the etiology of m.i.

III. Metabolism and Excretion

A. Mice

In 1954, Wase et al. (840) found in a study of Ni^{2+} metabolism using the isotope ^{63}Ni (for experimental details, see page 95 , Biochemical Data II, B2) that most of the ^{63}Ni was excreted via the feces in the first eight hours and that urinary excretion reached a maximum at four hours after administration (see Table 110).

Table 110.

Excretion of Nickel by the Mouse (840)

Time after administration of Ni hr.	Excretion rate	
	Urine counts/min./hr.	Feces counts/min./hr.
2	91	815
4	494	1402
8	104	8463
12	149	139
24	69	49
48	33	165
72	47	114

B. Rats

1. In 1950 Phatak and Patwardhan (591) fed rats various dosages of three Ni test materials; Ni carbonate, Ni soaps of mixed acids of refined arachis oil and Ni catalyst suspended in oil (for experimental details see page 33, Biological Data II, E1).

The observations, summarized in Table 111, were:

a) Approximately 71 to 91% of ingested Ni was found in the feces.

b) The percentage of Ni in the feces depended on the Ni preparation fed: Ni soaps, 87.9%; Ni catalyst, 89.9%; and Ni carbonate, 74.4%.

c) The percentage of Ni found in the urine also varied with the preparation given: Ni soaps, 1.21%; Ni catalyst, 0.77% and Ni carbonate, 1.56%.

d) Within each group (25, 50 or 100 mg dietary Ni supplement), the level of Ni did not have any appreciable effect on the proportions excreted in either the feces or urine.

Table 111.

Metabolism of Nickel in Rats (591)

Group No. with mg. of Ni/100 mg. diet	Number of animals	Figures are for the whole of four day period				
		Food intake gm.	Ni intake mg.	Urine Ni mg.	Faeces Ni mg.	Retention Ni mg.
Nickel Carbonate						
I — 100	8	27·60	27·60	0·53	19·70	7·41
II — 50	8	39·73	19·87	0·24	15·18	4·45
III — 25	8	41·92	10·54	0·16	7·98	1·17
Nickel Soap						
I — 100	4	39·49	39·49	0·43	35·00	4·04
II — 50	4	37·72	18·86	0·22	16·25	2·39
III — 25	4	39·42	9·85	0·14	8·75	0·99
Nickel Catalyst						
IV — 100	4	38·35	38·35	0·30	34·75	3·30
V — 50	4	41·87	20·94	0·13	18·44	2·39
VI — 25	4	42·62	10·66	0·09	9·69	0·87

2. In 1952, Phatak and Patwardhan (592) determined the intake and excretion of Ni in the urine and feces of rats at 4, 8, 12 and 16 months of continuous feeding on Ni-containing diets (for experimental details, see page 61, Biological Data III, B1). After the balance studies, the rats were put on a Ni-free diet.

The results are shown in Table 112. It was observed that:

a) Ni is eliminated from the body within a short time after removal from the diets.

b) Urine and feces became Ni-free in rats fed Ni for four months within 15 days of being on Ni-free diet; but it took 30 to 40 days for rats on Ni diet for 12 to 16 months.

Table 112.

Excretion of Nickel After Discontinuing the Nickel Diet (592)

(Figures are for 4 days' collection and are average of 4 rats)

Period	MG. OF NICKEL EXCRETED IN URINE & FAECES AFTER						
	Immediately after stopping nickel diet	10 days	15 days	20 days	25 days	30 days	40 days
After 4 months							
Urine	0·146	0·130	nil	—	—	—	—
Faeces	0·[illegible]	nil	nil	—	—	—	—
After 8 months							
Urine	0·155	—	0·150	—	0·062	0·036	nil
Faeces	0·092	—	0·009	—	nil	nil	nil
After 12 months							
Urine	0·119	0·160	—	0·050	—	nil	nil
Faeces	0·024	0·017	—	nil	—	nil	nil
After 16 months							
Urine	0·135	0·100	—	0·050	—	nil	nil
Faeces	0·068	0·016	—	nil	—	nil	nil

c) Ni remained in feces 10 to 15 days after its removal from the diet.

d) After discontinuing the Ni diet, urine was Ni-free within 40 days and feces within 20 days.

The rats were killed after the urine and feces were Ni-free and the tissues analysed for Ni. All were found Ni-free except for the kidneys (see Table).

Table 113.

Retention of Nickel in the Kidney of the Rat (592)

Period, months	No. of rats used	No. of rats showing nickel in kidney	Amount of nickel in kidney, mg./100 g.
4	4	—	—
8	4	2	0·54-0·71
12	4	3	0·09-0·16
16	4	2	0·14-0·16

3. In 1959, Kocher et al. (376) carried out tests on the excretion of $NiSO_4$ in rats injected with 1 and 2 mg in a 1% solution s.c. The major portion of the administered Ni was excreted in the urine during the first 24 hours. The values of excreted Ni in the feces were in the microgram/100 g range.

4. In 1960, Selivanova et al. (684) studied the distribution and excretion of Ni in mice, rats and rabbits (for a description of the experiments see page 93, Biochemistry Data II A).

With respect to Ni excretion in rats and rabbits injected i.v. with metallic Ni, it was observed that:

a) Ni excretion began on the second and third day after injection, with the peak on the seventh day.

b) After nine or ten days, no Ni was excreted.

c) The amount excreted in the feces was 400 to 600% greater than in the urine. (See Figure 11.)

It was found that when 50 to 1200 mg/kg metallic Ni was administered p.o. to mice and rats, the bulk of the Ni was not absorbed but was excreted in the feces.

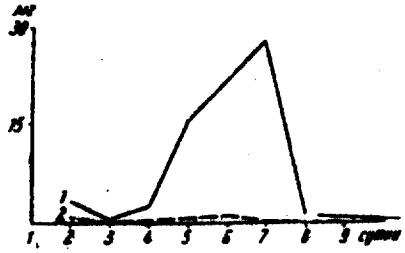

Figure 11. Curves of Nickel Excretion With Feces (1) and Urine (2) From a Rat that Received 500 mg/kg of Metallic Nickel Intravenously. (684)

5. In 1965, Payne (unpublished paper) studied the retention and excretion of $NiCl_2$ and NiS in rats injected s.c. Both compounds tested contained ^{63}Ni. The results are summarized in Tables 114, 115, 116, and 117, from unpublished paper.

It was observed that:

a) The recovery of $NiCl_2$ in the first three days after administration was generally about 80%.

b) The ratio of Ni in the urine to that in the feces was 10:1.

c) NiS was excreted at a significantly lower rate than the chloride.

Non-radioactive Ni_3S_4 (less soluble in H_2O than NiS) implanted in the necks of two rats was excreted more slowly than either $NiCl_2$ or NiS.

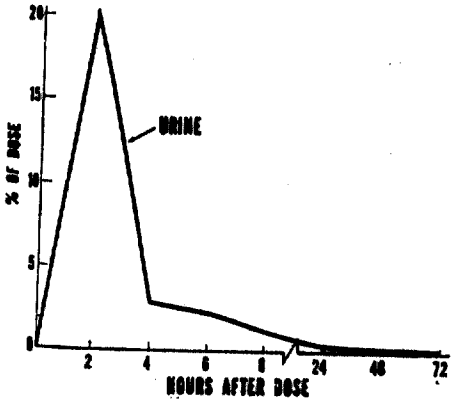

Figure 13. Average Hourly Urinary Excretion of Ni Following a Single Intravenous Dose (705)

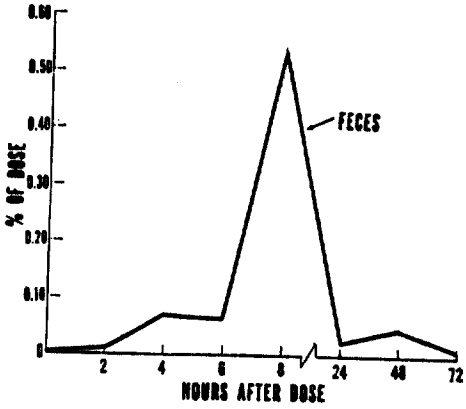

Figure 14. Average Hourly Fecal Excretion of ^{63}Ni Following a Single Intravenous Dose. (705)

C. Dogs

1. In 1937, Caujolle (113) investigated the biliary excretion of Ni in chloralosed dogs with choledochal fistulas. The injections of $NiCl_2$ in warm physiologic serum were administered i.v. in the central tip of the saphena.

The experimental data and results for ten animals are summarized in Table 118. The author concluded that under the experimental conditions the biliary excretion of Ni was relatively constant and quantitatively minimal.

2. In 1939, in a subsequent experiment with dogs, Caujolle and Canal (112) injected dogs with $NiCl_2$ and metallic Ni in various doses. The data for excretion for five of the animals studied are given in Tables 119, 120, 121, 122, 123, and 124. The authors concluded from their observations that:

a) The biliary elimination of Ni was always minimal.

b) The urinary elimination was generally very great.

c) Small quantities of the metal were seen to pass into the excreted froth.

d) The feces may contain Ni.

e) All the excretory organs collaborate in Ni elimination.

Table 114

Recovery of Nickel from Rats in Three Days Following Injection of Nickel Chloride (Payne, Unpublished Paper)

Injection No. and Site	Carrier Nickel	Sex	% Recovery		
			Urine	Feces	Total
1 Rt. Pleural Cavity	0	Female	85.0	9.8	94.8
		Male	65.5	16.1	81.6
2 Rt. Pleural Cavity	0	Female	83.4	7.8	91.2
		Male	75.4	8.4	83.8
3 Neck	0	Female	48.7	5.8	54.5
		Male	41.3	3.1	44.4
4 Neck	0	Female	6.13	22.4	83.7
		Male	85.5	4.1	89.6
5 Neck	0	Female	69.8	7.4	77.2
		Male	69.4	11.1	80.5
6 Rt. Pleural Cavity	3.1 mg 5.0 mg	Female	30.5	29.9	60.4
		Male	58.9	4.7	63.6
7 Rt. Pleural Cavity	3.1 mg 5.0 mg	Female	47.6	0.3	47.9
		Male	78.2	0	78.3

Table 115

Recovery of Nickel from Rats Following the First Injection of Nickel Chloride (Payne, Unpublished Paper)

Injection Site	Sex	Carrier Nickel	Days After Injection	% Cumulative Recovery Urine	Feces	Total
Rt. Pleural Cavity	Female	None	3	85.0	9.8	94.8
			8	86.9	11.3	98.2
Rt. Pleural Cavity	Male	None	3	65.5	16.1	81.6
			8	66.3	17.0	83.3

Table 116

Recovery of Nickel from Rats Following the Third Injection of Nickel Chloride (Payne, Unpublished Paper)

Injection Site	Sex	Carrier Nickel	Days After Injection	% Cumulative Recovery Urine	Feces	Total
Neck	Female	None	3	48.7	5.8	54.5
			7	49.9	6.5	56.4
			14	50.0	6.5	56.5
Neck	Male	None	3	41.3	3.1	44.4
			7	42.4	3.8	46.2
			14	42.7	3.8	46.5

Table 117.

Recovery of Nickel in Three Day Period Following Subcutaneous Administration in Rats (Payne, Unpublished Paper)

Compound	Sex	% Nickel Recovery Urine	Feces	Total
Nickel Chloride	Female	69.8	7.4	77.2
	Male	69.4	11.1	80.5
Nickel Sulfide NiS	Female	21.0	0.6	21.6
	Male	17.2	5.0	22.2

6. In 1968, Smith and Hackley (705) studied the excretion of Ni when 5 μCi ^{63}Ni was administered i.v. via the saphenous vein to five female Sprague-Dawley rats (218 ± 26 g).

The results are shown in Figures 12, 13, and 14. It was observed that:

a) Over 60% of the injected dose of ^{63}Ni was excreted by the urine within 72 hours.

b) During the same period, less than 6% was found in the feces.

c) Urinary excretion peaked at two hours following injection.

d) Fecal excretion peaked at eight hours following injection.

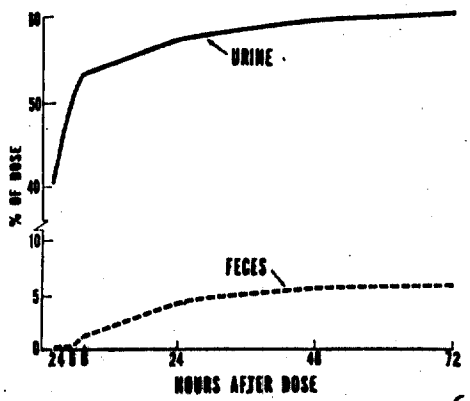

Figure 12 Accumulated Excretion of ^{63}Ni via the Urine and Feces Following a Single Intravenous Dose. (705)

Table 118

Biliary Excretion of Ni in Dogs (113)

Number	Weight in kg	Anesthetics used	Quantities of nickel used in mg		Actual duration of the experiment	Volume of bile collected in cm^3	Total quantity of Ni present in the collected bile in mg
			total	per kilogram			
1	18	morphine + chloralose	128.80	20.3	1 h. 38 (†)	2.0	None
2	25	chloralose	422.00	17.0	2 h. (†)	(*)	Very slight traces
3	15	chloralose	354.00	22.9	1 h. 20 (†)	1.1	1.00
4	17.5	morphine + chloralose	130.50	7.45	7 h. 50	21.0	0.20
5	9	morphine + chloralose	87.37	9.7	8 h. 13	4.2	Very slight traces
6	15	chloralose	150.00	10.0	7 h. 48	env. 20	0.15
7	23	chloralose	569.85	24.8	9 h. 29	20.3	< 1.00
8	18	chloralose	455.00	25.3	8 h.	10.1	0.89
9	16.5	morphine + somnifene	455.00	27.5	6 h. 40	11.5	0.46
10	19	morphine + somnifene	852.60	44.9	8 h. 20	3.0	< 0.10

* Determination was done in 1 cm^3 of bile obtained by the fistula, and on the gall bladder and its contents, samples at autopsy.

Table 119.

Total 852 mg Metallic Ni Injected i.v. (112)

Excreta	Quantity Collected	Total Ni in mg.
Urine (puncture)	32.5 cm^3	0.10
Bile from fistula	less than 1 cm^3	0.10
Bladder and gall bladder	28.5 g	0.60
Fecal matter	about 100 g.	1.3

Table 120.

Total 455 mg Metallic Ni Injected i.v. (112)

Excreta	Quantity Collected	Total Ni in mg.
Urine (autopsy)	about 50 g	29.4
Bile from fistula	22 g	0.46
Bladder and gall bladder	11.5 cm^3	0.40
Fecal matter	40 cm^3	0.5

Table 121.

Total 366 mg Metallic Ni Injected i.v. (112)

Excreta	Quantity Collected	Total Ni in mg.
Bile from fistula	2 cm^3	0
Bladder and gall bladder	48 g	traces
Urine from probe	11.5 cm^3	1.42
Bladder urine	2.6 cm^3	1.82

Table 122.

A Total of 88.9 mg Metallic Ni Injected i.v. (10 mg/kg) (112)

Excreta	Quantity Collected	Total Ni in mg.
Bile from fistula	4.2 cm^3	Very slight traces
Bladder and gall bladder	9 g	traces
Urine	35 cm^3	23.7
Fecal matter	about 200 g	traces
Vomited matter	about 100 g	Very slight traces

Table 123.

A Total of 345 mg Metallic Ni Injected i.v. (112)

Excreta	Quantity Collected	Total Ni in mg
Bile from fistula	1.1 cm^3	1.0
Bladder and gall bladder	18 g	0.5
Urine	28 cm^3	21
Saliva	5 cm^3	Very clear traces

Urine became mahagony colored at the end of the experiment.

Table 124.

A Total of 570 mg Metallic Ni Injected i.v. (112)

Excreta	Quantity Collected	Ni in mg p. 100 g
Bile from fistula	22.1 cm^3	1.00
Bladder and gall bladder	33 g	Very slight precipitate
Urine from probe and bladder urine	570 cm^3	98.13

3. In 1957, Tedeschi and Sunderman (774) examined Ni metabolism in dogs under normal conditions and following exposure to $Ni(CO)_4$.

Healthy dogs were exposed to $Ni(CO)_4$ vapors for 30-minute periods in concentrations ranging from 0.2 to 1.0 mg/liter. The results of Ni balance studies before exposure are shown in Table 125. The results show that:

a) The amount of Ni excreted in the urine and feces is almost equal to the intake in food.

b) An average of 90% was excreted in the feces and 10% in the urine.

Table 125.

Nickel Balance Studies
(Before Exposure to Nickel Carbonyl) (774)

Dog	3-Day Period	Ni in Food, Mg.	Ni in Stool, Mg.	Ni in Urine, Mg.	Balance, Mg.
1	1	0.79	0.72	0.04	+0.03
	2	0.48	0.44	0.03	+0.01
	3	1.34	1.21	0.07	+0.06
	4	0.88	0.83	0.05	0.0
2	1	1.21	1.05	0.07	+0.11
	2	1.39	1.19	0.07	+0.13
	3	1.09	1.19	0.10	+0.00
3	1	1.38	1.14	0.08	+0.16
4	1	1.54	1.36	0.13	+0.05
Average S.D.		1.12±0.16	1.01±0.44	0.07±0.03	

The amounts of Ni excreted after exposure to $Ni(CO)_4$ are shown in Table 126. The results show that:

a) There was a significant ($P < 0.01$) increase in Ni excretion in the urine during the first three-day period after exposure as compared with the control period.

Table 126.

Nickel Balance Studies
(After Exposure to Nickel Carbonyl) (774)

Dog	3-Day Period	$Ni(CO)_4$, Mg./L.	Ni in Food, Mg.	Ni Inhaled, Mg.	Ni in Stool, Mg.	Ni in Urine, Mg.	Intestin Ejecta, Mg.	Balance
1	1	0.2	1.40		1.57	2.98	−3.2	
2	1	0.2	0.85		1.50	3.86	−1.5	
	2		1.63		1.65	0.22	0.2	
3	1	1.0	0.55		1.12	3.71	−4.3	
	2		1.61		1.70	0.27	−0.4	
4	1	1.0	0.78		1.17	3.32	−3.7	
	2		1.96		2.22	0.29	−0.6	
5	1	0.4	2.52	2.25	1.78	2.10	−1.4	+0.9
			2.24		2.90	0.10	−0.9	−0.9

b) There was no significant difference between Ni ingestion and excretion in the feces during this same period (see Figure 15).

c) In days four to six following exposure, the amount of Ni in urine tends to return to pre-exposure levels.

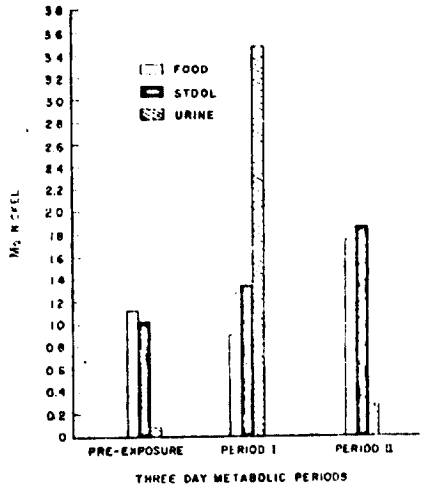

Figure 15 . Nickel Balance Studies in Dogs Before and After Exposure to Nickel Carbonyl (774)

As can be seen with dog 5 in Table 126, about 99% of the ingested and inhaled Ni was eliminated within six days in the urine and feces, and there was no significant retention of Ni in the body.

The authors concluded that the observation of a sharp increase in Ni excretion in the urine of dogs immediately after acute exposure is of major practical importance because in some cases of accidental poisoning, symptoms can remain latent for from eight to ten days by which time in the case of Ni, for example, the level in urine is practically normal.

D. Calves

1. In 1971, O'Dell et al. (551) studied the excretion of Ni in 12 male Holstein calves fed supplementary dietary Ni (as $NiCO_3$) at levels of 0, 62.5, 250 and 1000 ppm for five days.

The results are summarized in Table 127. They showed that:

a) The primary route of Ni excretion was in the feces.

b) Fecal material contained from 22 to 51 times as much Ni as urine.

c) Animals receiving 250 ppm Ni in the diet had the largest total daily fecal Ni excretion.

d) The fecal Ni included both unabsorbed and re-excreted Ni because the analysis cannot distinguish between them.

e) Of the total excreted Ni, animals receiving 62.5, 250 and 1,000 ppm Ni excreted, respectively, 97.3%, 98.1% and 95.8% in the feces.

Table 127.

Effect of Dietary Nickel Level on Average Nickel Content of Excreta Collected Over a 5-Day Period (551)

	Level of nickel supplementation, ppm				
Item	0	62.5	250	1,000	SE[a]
Urinary Ni					
μg/ml	0.08	1.86	6.18	33.90	.....
Total daily excretion, mg	0.47[b]	7.16[b]	24.75[c]	45.81[d]	5.1
Fecal Ni					
μg/g dry matter	5.40	158.25	713.76	2299.78	...
Total daily excretion, mg	9.83[b]	260.56[b]	1285.30[c]	1020.90[d]	80.
Total excreta, mg Ni	10.30[b]	267.72[b]	1310.05[c]	1066.21[d]	85.
Supplemental Ni intake, mg daily	.....	335.37	1325.62	1414.20	...

[a] Standard error of a mean with three animals per treatment.
[b-d] Mean values within a row that are not followed by the same superscript are significantly different ($P<.05$).

E. Humans

1. In 1941, Kent and McCance (342) injected two normal men with $NiCl_2$ i.v. daily for one week. The results are summarized in Table 128. These results show that 60 to 70 percent of Ni ingested in food was excreted in the urine. Injected Ni was excreted slowly by the kidney.

2. In 1953, Kincaid (360) noted that Drinker and coworkers (reference in original paper) had results at variance with those reported by Kent and McCance (342) in this Section, E1) in that Ni was almost never detected by Drinker and associates in normal urine. Most of the Ni ingested in food cooked in Ni utensils was found to

be excreted in the feces: as much as 30 mg/day compared with 0.8 mg/day for normal subjects. The author noted that the values for concentrations of Ni in urine reported by Kent and McCance were also higher than his own findings (normal range 0.00 to 0.10 mg/liter). In humans exposed to $Ni(CO)_4$, however, the amount of Ni excreted in urine was above normal.

Table 128.

The Absorption and Excretion of Nickel (342)

Subject	Length of period days	Ni intake mg./period: Injected	Ni intake mg./period: In food	Ni excretion mg./period: In urine	Ni excretion mg./period: In faeces	Balance mg.	Ni 'recovered' mg.
E. B.	7		2·25	1·67	0·72	- 0·14	
	7	9	1·99	3·42	0·69	+ 6·88	3·8
	7		2·67	3·16	1·19	- 1·68	
N. K.	7		—	2·29	1·20	—	
	7	20	5·51	6·70	1·33	+17·48	
	4		2·21	2·88	0·59	- 1·26	
	7		3·43	3·48	2·11	- 2·16	7·4
	7		3·20	2·61	2·05	- 1·46	

IV. Effects on Enzymes and Other Biochemical Parameters

A. In Vitro

1. In 1935, Hellerman and Perkins (260) showed that Ni^{2+} activated arginase. (For details of method, see original paper.)

The initial reaction mixture to which 3 mg $Ni(NO_3)_2 \cdot 6H_2O$ was added consisted of 5 ml arginase, 4 ml H_2O and 10 ml phosphate (1 M, pH 7.5); the volume of arginase-arginine digestion mixture was 21 ml. The effect of Ni^{2+} on arginase activity, expressed as ml of 0.02 N HCl (corrected) equivalent to N H_3 in 10 ml filtrate after urease action: 0.02 N HCl corresponding to initial activity; 3.06 ml; 0.02 N HCl corresponding to activity, 5.61 ml.

2. In 1936, Whitnah et al. (858) studied the effect of added Ni^{2+} (added as the sulfate) on vitamin C in milk. The amount added, the times at which vitamin C was tested, and the amounts found are shown in Table 129. It was observed that:

a) The effects of 1.0 ppm added Ni were more pronounced in the pasteurized than in the raw milk form.

b) The average effect was as great after two hours storage as after 24 hours.

c) The effect in different samples of milk varied widely.

Table 129

Vitamin C in Pasteurized Milk to which Ni was Added (858)

Metal Added P.P.B.	Average Extra Loss[a]	Average Mg./l	Test Number 1	2	3	4	5	6	7	8
			Vit. C 24 hrs. after past. (mg./l)							
0	0	10.3	12.9	12.9	11.1	6.8	7.5	8.0	11.4	11.4
1000 nickel	19	7.9					4.7	6.1	10.1	10.8

[a]The losses were calculated as average percentages of the individual mg/l of vitamin C in the samples to which no metal was added. Losses of less than 20 percent have doubtful significance.

3. In 1949, Speck (713) showed that Ni^{2+} activated oxalacetic carboxylase. The enzyme prepared from parsley roots was used to study the effect of cations on the enzymatic decarboxylation of oxalacetate. It was found that the rate of decarboxylation in the presence of enzyme plus Ni^{2+} was greater than that in the presence of cation alone, of enzyme alone or of cation plus heat-inactivated enzyme.

4. In 1952, Kertesz (345) found that 0.00005 m M Ni^{2+} significantly accelerated the enzymic oxidation of 0.9 mg tyrosine in 0.05 mg Dopa. It was found that while the first phase of tyrosine oxidation (the transformation of tyrosine in Dopa) was considerably accelerated by excess Ni^{2+}, the second phase (the transformation of Dopa in its o- quinone) was not activated by Ni^{2+}.

5. In 1952, Forbes and Smith (193) reported on the marked inhibitory action of Ni salts on the production of acid by saliva containing either glucose or sucrose. Sucrose was added to saliva to give a 5% concentration and varying amounts of the salts tested were added to aliquots of the sucrose-saliva mixture (except for controls). The results are shown in Table 130 and show that:

a) Ni exerted marked inhibitory action on acid production.

b) This inhibitory action is primarily a function of metal content.

The authors continued their studies (193) by investigating the bactericidal action of Ni salts on the acidogenic organisms in saliva. The results are shown in Table 131. It was found that at a concentration of 0.002 M $NiCl_2$, the acidogenic

organisms in saliva were either destroyed or completely inhibited when exposed for 24 hours. Even a 15-minute exposure resulted in the apparent destruction of many of the organisms.

Table 130

Effect of Ni Salts Upon Acid Production in Saliva (193)

Time of Incubation hrs.	Concentration of Metal Mg/100 Ml 6 (pH)	4 (pH)	2 (pH)	1 (pH)	0 (pH)	Substance Used
23	7.0	6.9	6.7	6.8	4.1	Nickel propionate
51	7.1	6.7	5.5	4.9	3.7	
24	7.2	7.4	7.5	7.2	4.2	Nickel chloride
48	8.0	8.1	8.0	6.1	4.0	
24	7.3	7.4	7.4	6.7	4.4	Nickel iodide
50	7.6	7.5	7.3	5.3	4.0	

Table 131

Bactericidal Action of Nickel Chloride on the Acidogenic Organisms in Saliva (193)

DURATION OF INCUBATION (HOURS)	CONCENTRATION OF INHIBITOR TIMES 10^{-3} M 2.0 (pH)	1.5 (pH)	1.0 (pH)	0 (pH)	TIME SALIVA IN CONTACT WITH INHIBITOR
48	--	6.8	4.6	4.5	$NiCl_2$ for 15 minutes
48	--	7.9	4.7	4.4	As above for 1 hour
48	--	8.0	6.5	4.3	As above for 23 hours
48	5.5	5.1	4.7	4.4	As above for 15 minutes
48	5.9	5.1	4.7	4.4	As above for 1 hour
48	8.0	7.6	5.2	4.4	As above for 24 hours

6. In 1956, Roth (631) found that Ni^{2+} (sulfate) inhibited pancreatic RNase reaching 72% with 1.6×10^{-3} M $NiSO_4$ (see Table 132). When Ni^{2+} was added to cell-free homogenates of three-day cultures of Tetrahymena pyriformis W to give a final concentration of 8.0×10^{-4} M, it was found to be inhibitory to RNase activity.

The author concluded that these results were consistent with the theory that the inhibitory effect of Ni^{2+} on cell division in Tetrahymena (described in original paper) is due to the inhibition of RNase and even perhaps DNase activity which in turn prevents the normal breakdown and turnover of nucleic acids.

Table 132.

The Effect of Various Concentrations of Ni^{++} on the Activity of Crystalline Pancreatic Ribonuclease (631)

Average of Triplicate Experiments		
Final Conc. of Metal Ion M	Amount of Enzyme per 25 ml soln. γ	Inhibition by Ni^{++} %
1.6×10^{-4}	2	9
4×10^{-4}	2	28
8×10^{-4}	2	56
1.6×10^{-3}	2	72
8×10^{-4}	1	64

7. In 1958, Hatem and Champy (251) suggested from previous observations that organic carcinogens blocked histamine, that metallic carcinogens might act similarly. It was found that in aqueous solutions, Ni salts (chloride, nitrate and sulfate) complexed with histamine-forming soluble compounds. The authors reported verifying *in vivo* (reference in original paper) that nerve histamine fixes Ni.

8. In 1958, Szilagyi *et al.* (750) investigated the effect of Ni^{2+} ion on epinephrine and acetylcholine using isolated frog heart. Heart function was found to be considerably depressed by 100 μg Ni^{2+} (as $NiSO_4 \cdot 7H_2O$). After infusion with the Ni salt, 0.05 μg epinephrine was found to be far less effective than with controls. The adrenolytic effect of Ni^{2+} was only exerted at doses high enough to depress heart function. The effect of acetylcholine on heart function was not influenced by Ni^{2+}.

9. In 1959, Wacker and Vallee (833) found that Ni was one of the metals present in significant concentrations in RNA preparations from phylogenetically diverse sources such as pancreas, supernatant of pancreas, thymus of calf, horse kidney, rabbit reticulocytes, *Euglena gracilis* and rat liver (see Table 133). The authors suggested that metals may bear a functional relationship to protein synthesis and the transmission of genetic information.

Table 133.

Ni Content of RNA from Various Sources (in μg per g of RNA) (833)

Source	Ni
Calf Pancreas	130
(S-RNA) Calf Pancreas	18
Calf Thymus	74
Horse Kidney	44
Rabbit Reticulocyte	51
Euglena Gracilis	60
Rat Liver *	64

* Procedure of (35)

10. In 1960, Hatem and Champy (252) continued their investigation into the relationship between the complexing of Ni by histamine and carcinogenesis. In this study they investigated what the effect of a salt of ethylenediaminetetra-acetic acid (EDTA) would be on the Ni-histamine complex. The salt of EDTA was found to free the histamine from a solution containing the Ni-histamine complex.

The authors noted that it had been found that this salt of EDTA (monocalcium disodium salt) reduced cancer formation in the respiratory tract of workers exposed to Ni powder. They concluded that the action of the EDTA was to reduce the blocking of histamine by the carcinogen, nickel.

11. In 1962, Vulpis and Georgino (831) found that when Ni^{2+} (as $NiCl_2 \cdot 6H_2O$) was added to plasma there was a delay in the coagulation process consisting of an increase in maximal amplitude. Ni^{2+} was found to produce marked effects in small amounts (see Table 134).

12. In 1964, Cotton (136) investigated Ni-protein complexes with reference to the nature and number of binding sites occupied by the metal using mainly crystalline bovine serum albumin. Other proteins studied were human gamma globulin, commercial casein and gelatin, pseudo-globulin and cyanide and sulfide-kerateines. Using the technique of equilibrium dialysis, it was found that:

a) The Ni-protein complex has a low stability,

b) The amount of Ni bound by the protein depended on concentration of free Ni ions, pH and the particular protein used in the study,

c) Carboxyl and amino groups were most probably the binding sites of Ni ions to protein.

Table 134

Effect of $NiCl_2$ on Reaction Time and Maximal Amplitude of t.e. Graphic Tracing. The cation amount is referred to the 0.36 ml volume reached in the cuvet. For every combination a parallel experiment with saline was carried out; the numbers within brackets correspond to the results so obtained. The mean value of 3 determinations is given. (831)

Tested Salts	Metal Cations γ Ions	r Values mm	ma Values mm	Final pH of Mixture
$NiCl_2 \cdot 6H_2O$	Ni^{++} 0.124	75 (11.5)	37 (60)	7.6

13. In 1967, Dixit and Lazarow (155) studied the effect of Ni^{2+} on the metabolism of glucose by rat adipose tissue (epididymal fat pad) using ^{14}C labeled glucose. It was found that:

a) Ni^{2+} stimulated glucose oxidation and incorporation into lipids which was most strongly pronounced at 10^{-2} M (see Figure 3 in original article).

b) Both glucose oxidation and incorporation into lipids were enhanced to a greater extent in the preaence of gelatin than in albumin (P <0.001). (See Figure 16 .)

c) Ni enhanced incorporation of glucose into glycogen but to a much smaller extent than insulin. (See Figure 16 .)

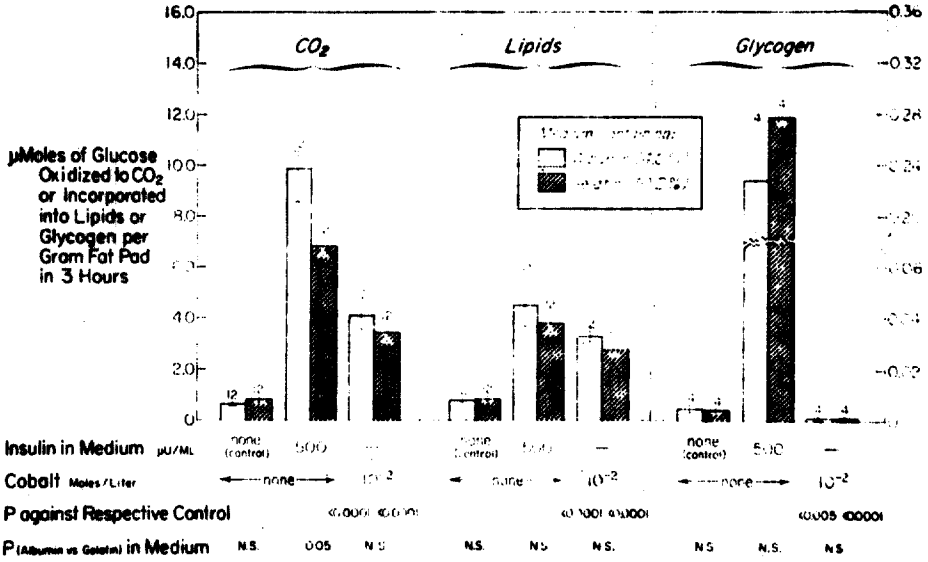

Figure 16 . A Comparative Effect of Colbalt (10^{-2}M) on the Metabolism of Glucose by Rat Epididymal Fat Pad in Media Containing High (4.0% Albumin) or Low Protein (0.2% Gelatin). (155)

14. In 1967, Cormane et al. (134) found that the alkaline phosphatase activity of the interstitium of myo- and endometrium was much increased when guinea pig uterus was exposed to > 1 mmol Ni^{2+}/liter for a few minutes. This concentration was in excess of that required for maximum concentration and maximum absorption. The authors pointed out that very strong enzyme activity was found at the cell membranes in the endometrium, where it was not present before. The authors concluded that alkaline phosphatase activity was greatly increased by Ni^{2+} but only when present in excess.

15. In 1968, Fuhrmann and Rothstein (209) found that Ni^{2+} inhibited the enzyme, alcohol dehydrogenase from yeast. The inhibition at 0.5 mM was about 85%. The authors noted that Ni^{2+} has been found to only partially inhibit glucose metabolism and glucose uptake even at high concentrations. They concluded from their study a possible explanation based on transport into the cell and subsequent inhibition of alcohol dehydrogenase.

B. Mice

In 1969, Weber and Reid (846) fed 1100 and 1600 ppm Ni (as Ni acetate) to young growing mice (see page 32 Biological Data II, D3 for experimental details). Metabolism and enzyme activities studies showed that (see Table 135):

a) Bone metabolism was not markedly affected by Ni ingestion.

b) For mice fed either 1100 or 1600 ppm, there was a significant decrease ($P < 0.05$) in cytochrome oxidase and isocitric dehydrogenase activities of liver homogenates.

c) At 1600 ppm Ni level, NADH cytochrome C reductase activity of liver homogenates was significantly decreased in activity ($P < 0.05$).

d) At 1600 ppm Ni level, cytochrome oxidase and malic dehydrogenase of heart homogenates were significantly decreased ($P < 0.05$) in enzyme activity.

e) At 1600 ppm Ni level, malic dehydrogenase was significantly ($P < 0.05$) decreased in activity in kidney homogenates.

f) Ni did not appear to affect any given enzyme system, but did decrease the activity in both the Krebs cycle and the electron transport systems.

g) All other tissues tested for cytochrome oxidase, malic, isocitric and succinic dehydrogenase were unaffected.

The authors concluded that results of the enzyme activities studies indicated that Ni exerted its influence in the kidney and liver where it is known to concentrate.

Table 135.

Effect of Nickel Acetate on the Enzyme Activity of Both Male and Female Mice (846)

Enzyme system[a]	Tissue	Dietary levels of nickel added: 0 ppm	1100 ppm	1600 ppm
Cytochrome oxidase	Liver	66[b]	39[c]	31[c]
	Kidney	79[b]	89[b]	78[b]
	Heart	50[b]	43[b]	21[c]
Malic dehydrogenase	Liver	87[b]	86[b]	99[b]
	Kidney	159[b]	128[b]	65[c]
	Heart	112[b]	111[b]	95[c]
Isocitric dehydrogenase	Liver	51[b]	37[c]	37[c]
	Kidney	29[b]	26[b]	6[b]
	Heart	42[b]	40[b]	30[b]
Succinic dehydrogenase	Liver	57[b]	42[b]	54[b]
	Kidney	4.4[b]	3.1[b]	0.8[b]
NADH cytochrome C reductase	Liver	79[b]	70[b]	55[c]

[a] Enzyme activity calculated as delta O.D./min./gm. of protein.

[b, c] Means with different superscript letters differ significantly ($P<.05$).

C. Rats and Guinea Pigs

1. In 1930, Pratt (607) investigated whether Ni catalytically destroyed vitamins A, B and C in milk by feeding rats (390) and guinea pigs (140) adequate rations supplemented by raw milk, milk pasteurized in glass or milk pasteurized in a Ni container (15 ppm Ni in milk) to supply the vitamins.

The results showed that:

a) Vitamin A was not appreciably destroyed by pasteurization in either glass or Ni.

b) The antineuritic factor of vitamin B complex was partially destroyed by pasteurization but there was no evidence that Ni catalyzed the destruction.

c) Vitamin C was partially destroyed by pasteurization but no increase of destruction due to Ni was apparent.

2. In 1957, Guillet (237) studied siderosis caused in rats by Ni poisoning. Adult albino Wistar rats received 2 mg $NiCl_2$ i.p. daily. As many as 60 to 100 injections were given. Large increases in iron deposits were found in the spleen, lymph nodes, liver and in particular, the kidney.

3. In 1962, Sunderman et al. (733) reported that their preliminary data indicated that Ni bound to lung and liver RNA was increased following exposure of rats to $Ni(CO)_4$.

In 1963, Sunderman (736) continued the investigation of the influence of $Ni(CO)_4$ inhalation on the Ni content of RNA. The results are shown in Table 136. It was found that the concentration of Ni in the NaCl-precipitable lung RNA increased while that in the NaCl-soluble fraction decreased following exposure of rats to $Ni(CO)_4$.

Table 136

Concentration of Nickel in Lung and Liver Ribonucleic Acid (RNA) Following Inhalation of Nickel Carbonyl* (736)

Tissue	Preparation	Nickel Concentration†	
		Control Group	Exposed Group [$Ni(CO)_4$]
		µg./Gm. RNA	
Lung	NaCl-precipitable	110	270
	NaCl-soluble	310	230
Liver	NaCl-precipitable	59	160
	NaCl-soluble	120	110

* Exposure to 0.60 mg. of $Ni(CO)_4$ per 1. of air for 30 minutes.
† Mean of triplicate analyses.

4. In 1968, Joo (314) investigated whether ATPase is inhibited in the brain vessels after i.p. administrationsof $NiCl_2$. Ten rats were injected i.p. with $NiCl_2$ (0.25 g/kg dissolved in physiological saline) and killed at: 30 to 60 minutes, 3, 6, 12 and 24 hours. Using Padykula's method for ATPase activity (reference in original paper), it was observed that:

a) No ATPase activity was seen in 20 to 50 μ areas of capillary walls between 30 to 60 minutes after administration.

b) Between 3 to 6 hours, no ATPase activity in brain vessels was shown

c) After 12 hours, enzyme activity was detected in parts of the capillary wall.

d) After 24 hours, the ATPase in the animals given $NiCl_2$ was about the same as the controls.

e) There was no change in the activity of non-specific alkaline phosphatase.

The author concluded that $NiCl_2$ apparently inhibited ATPase specifically.

5. In 1968, Schroeder (670) gave rats 5 ppm Ni (as a soluble salt) in drinking water from weaning to 11 to 30 months of age. The mean serum cholesterol levels were found to be consistently low in both sexes given Ni (with all animals receiving 1 ppm Cr in their diets). The author concluded that there was a possibility Ni had anticholesterolgenic properties.

6. In 1969, Itskova et al. (303) administered Ni p.o. daily for seven months to 72 rats in doses from 5.0 to 0.0005 mg/kg. It was found that:

a) There was a reduction in the activity of the enzymes alkaline phosphatase and enterokinase in the intestinal contents as well as the scrapings of the mucous membrane at doses of 5 and 0.5 mg/kg Ni.

b) A reduction in the absorption of Ca and Mg (see Figure 17) was also noted in rats receiving 5 mg/kg ($P < 0.05$).

c) The maintenance of ascorbic acid in the liver was substantially reduced at this dose (up to 5.0 ± 0.86 mg % as compared to 9.1 ± 1.3 mg % in the controls, $P < 0.05$). There was some reduction of ascorbic acid maintenance in the adrenals.

Figure 17. The Absorption of Calcium (a) and Magnesium (b) in Percentages of the Introduced Dose in the Control (1) and During Introduction of Nickel in a dose of 0.005 (2) and 5 mg/kg (3). (303)

7. In 1970, Hebert (258) compared the arginase activity in Ni_3S_2-induced muscle tumors with that of normal muscle tissue. The tumors used in this study were randomly selected from a group of Fischer rats which received single i.m. injections of 10 mg Ni_3S_2. A definite enhancement of arginase activity was found in tumor tissues as compared to that of normal muscle. Tumor arginase activity was not as high as that found in liver tissues. The author noted that his findings agreed with those of Greenstein (reference in original paper) that the enzyme activity in tumors of rats and mice was below or between the range noted for normal tissues.

8. In 1970, Beach and Sunderman (045) studied the effect of $Ni(CO)_4$ on RNA synthesis by a chromatin-RNA polymerase complex prepared from lysed hepatic nuclei in order to localize the site of toxic action of $Ni(CO)_4$. Chromatin-RNA polymerase complex was prepared from the isolated hepatic nuclei of male Sprague-Dawley rats (180 to 200 g) injected i.v. with $Ni(CO)_4$ equivalent to 2.2 mg Ni/100 g BW. Untreated animals were controls.

The results given in Table 137 show that $Ni(CO)_4$ produced an average of 52% inhibition of RNA synthesis by the chromatin-RNA polymerase complex ($P < 0.001$).

In vitro effects of $Ni(CO)_4$ or $NiCl_2$ were studied with suspensions of chromatin-RNA polymerase complex from livers of nine untreated rats. The results given in Table 138 show that there was no significant effect on RNA synthesis by the chromatin-RNA polymerase.

Table 137.

Effect of $Ni(CO)_4$ Upon RNA Synthesis by Chromatin-RNA Polymerase Complex from Hepatic Nuclei (045)

	No. of rats	RNA synthesis (μmole CTP-^{3}H/10 min/g DNA) Mean ± S.E.	p
Controls	18	0.33 ± 0.03	
$Ni(CO)_4$[a]	18	0.16 ± 0.02	<0.001

[a] $Ni(CO)_4$ (2.2 mg Ni/100 g, i.v.) 6 hr before sacrifice.

Table 138.

RNA Synthesis by Chromatin-RNA Polymerase (045) Complex After In Vitro Additions of $Ni(CO)_4$ or $NiCl_2$

	Ni concentration in assay mixture (M)	No. of rat livers	RNA synthesis (% paired controls) Mean ± S.E.	p
Ni(CO) *in vitro*	1×10^{-5}	9	95 ± 9	>0.9
$NiCl_2$ *in vitro*	1×10^{-5}	9	104 ± 6	>0.9
[$Ni(CO)_4$ *in vivo*	3.4×10^{-6}	18	48 ± 6	<0.001]

The authors concluded that their study showed that the inhibition of RNA synthesis persisted after disruption of the hepatic nuclei and excluded inhibition owing to impaired transport of RNA precursors across the nuclear membrane. They made the additional point that because inhibition was not observed after in vitro additions of $Ni(CO)_4$ or $NiCl_2$ in greater concentrations than that by in vivo injection of $Ni(CO)_4$, inhibition of RNA synthesis was not just attributable to the presence of Ni.

D. Rats and Chicks

The question of whether or not Ni is an "essential mammalian trace metal" has been raised by several authors cited in this monograph (144 , 669, 673). Nielsen and Sauberlich in 1970 (537) suggested that "nickel has a physiological role in the chick".

In 1962, Schroeder et al. (673) defined essentiality as having "a normal role". The hypothesis that Ni was an essential trace metal was based on the following:

1. It is ubiquitous on both the earth's crust and in the oceans.
2. It is present in plants and animals.

3. Ni biological activity in vitro affects certain enzyme systems:
   a) It can displace beryllium from alkaline phosphatase and reactivate the enzyme.
   b) It activates arginase in vitro (along with cobalt, iron and manganese).
   c) It catalyzes decarboxylation of some amino acids and the saturation of unsaturated fats.
4. Ni has a low molecular weight and two interchangeable valences.
5. It is non-toxic to mammals orally except in "astringent doses".

In 1974, Nielsen and Ollerich (536) presented evidence that Ni is an essential nutrient for chicks and rats. They noted that "examination of the periodic table reveals that of the elements in the transition series from V (23) to Zn (30), Ni is the only one not generally accepted as essential for animals". (See Figure 18) attached.)

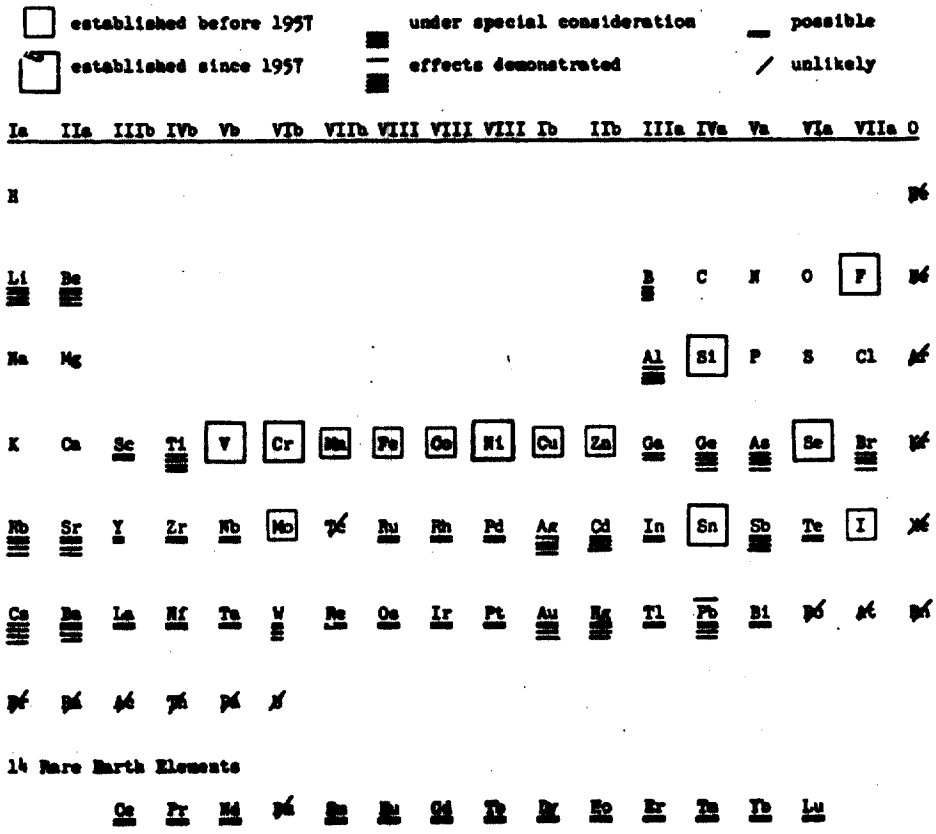

Figure 18 . Periodic System Distribution of Trace Elements of Known and Potential Importance for Warmblooded Animals. Status as of 1973. (668)

Nielsen and Ollerich (536) found that Ni deficiency in chicks and rats resulted in suboptimal liver function as evidenced in chicks by ultrastructural degeneration, reduced oxidative ability, increased lipid and a decreased phospholipid fraction. Ni deprived rats also showed a reduced oxidative ability in liver and abnormalities in the polysome profile. The authors concluded that their findings were consistent with Ni being an essential nutrient for chicks and rats.

E. Guinea Pigs

In 1962, Sobel et al. (706) found that when Ni^{2+} (as $NiCl_2 \cdot 6H_2O$) was injected i.p. in 10 guinea pigs at a dose of 4 μ M/100g, the six-hour urinary corticoid excretion was almost doubled.

V. Drug Interactions

A. Mice, Rats and Rabbits

1. In 1958, West and Sunderman (854) investigated the effect of calcium-disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$, Edathamil) in mice and rabbits exposed to $Ni(CO)_4$ vapors. The experiment with mice (10 mice per group) is summarized in Table 139. It was found that the mortalities in the groups receiving $CaNa_2EDTA$ did not differ significantly from those of controls.

Table 139.

Effect of Edathamil Calcium-Disodium on Mice Exposed to Nickel Carbonyl, 0.06 Milligrams per Liter (854)

Groups	$CaNa_2EDTA$ Dosage, Mg/Kg.	$CaNa_2EDTA$ Frequency of Administration	Mortality Ratios (3 Days) Dead/Treated
$Ni(CO)_4$			6/10
$Ni(CO)_4$+$CaNa_2EDTA$	40	2 doses daily—3 days	6/10
$Ni(CO)_4$			10/10
$Ni(CO)_4$+$CaNa_2EDTA$	200	2 doses daily - 2 days	9/10
$Ni(CO)_4$			9/10
$Ni(CO)_4$+$CaNa_2EDTA$	500	2 doses first day	10/10
$Ni(CO)_4$			8/10
$Ni(CO)_4$+$CaNa_2EDTA$	500	3 doses - first day	6/10

A similar experiment in which 7 healthy male albino rabbits (2.5 kg) were exposed to $Ni(CO)_4$ vapors and four given injections of $CaNa_2EDTA$ in dosages as high as 500 mg/kg BW had similar results. All of the animals (controls and treated) died

within 90 hours after $Ni(CO)_4$ exposure. No significant difference was found between the distribution of Ni in the organs (lungs, liver, kidneys and brain) of animals receiving $CaNa_2EDTA$ and controls. The amounts of Ni excreted in the urines of both experimental and control rabbits were about the same. It was concluded that $CaNa_2EDTA$ did not overcome the lethal effects of $Ni(CO)_4$.

In another experiment, Swiss albino mice (18 to 20 g) and Wistar albino rats were first injected i.p. with Ni nitrate in dosages from 0.5 to 2.5 mg/kg BW, then administered $CaNa_2EDTA$ i.p. in dosages from 100 to 600 mg/kg BW. The results showed that $CaNa_2EDTA$ did not provide protection against the toxic effects of lethal amounts of parenterally administered Ni nitrate.

2. In 1959, Kocher et al. (376) investigated the protective effect of 500, 1000 and 1500 mg/kg $CaNa_2EDTA$ administered i.p. to white mice simultaneously with 100 mg/kg $NiSO_4$ solution. The results (see Figure 19) showed that at all three dosages $CaNa_2EDTA$ had a significant ($P < 0.01$) protective effect. This finding is in disagreement with that of West and Sunderman (854) who found no protective effect of $CaNa_2EDTA$ with a parenterally administered Ni salt.

The observation of Kocher and coworkers that $CaNa_2EDTA$ had no significant effect on Ni excretion in urine was in agreement with West and Sunderman (see page 140). No effect of $CaNa_2EDTA$ on the excretion of Ni in feces was observed by Kocher and coworkers.

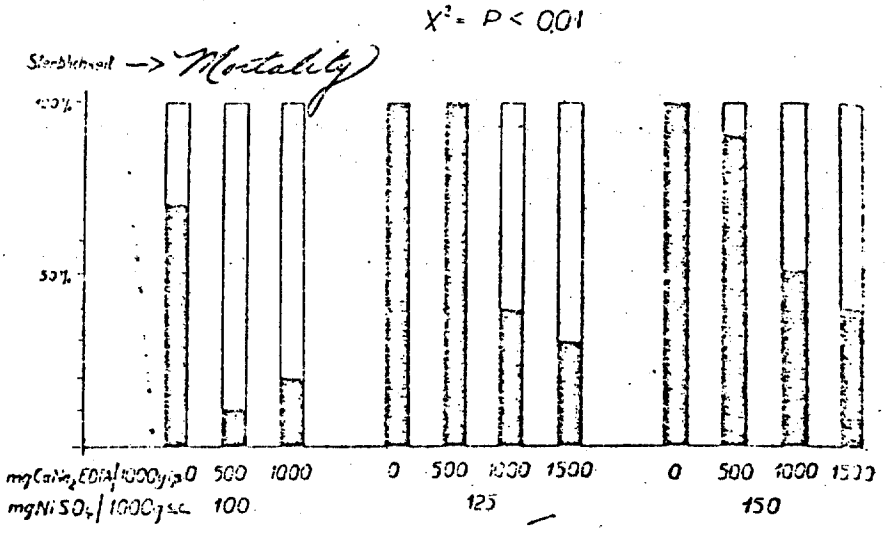

Figure 19. (376)

B Rats

1. In 1942, Griffith, et al. (229) found that when rats (male 20 to 26 days, 38 to 42 g) which were either administered Ni (as $NiSo_4 \cdot 7H_2O$) p.o. or i.p. were given cysteine i.p. either separately or simultaneously, the toxic effects of the Ni were largely neutralized (see Table 140).

Table 140.

Effect of Cysteine[1] on the Toxicity of Nickel in 40 g Male Rats (229)

Group	Nickel[2] Used	Procedure	No. of Rats	24-Hour Mortality
17	20	Per os	28	64
18	20	Nickel per os + intraperitoneal injection of 34 mg cysteine hydrochloride	12	50
19	20	Nickel per os + intraperitoneal injection of 17 mg cysteine hydrochloride after 0 and 3-1/2 hours	16	25
20	3	Intraperitoneal injection	7	14
21	6	Intraperitoneal injection	10	90
22	10	Intraperitoneal injection	6	86
23	10	Intraperitoneal injection of nickel-cysteine complex	10	0

[1] Cysteine hydrochloride and one equivalent of $NaHCO_3$ were used.

[2] Nickel-cysteine (1:3) complex containing 1.7 mg of cysteine hydrochloride and 0.9 mg of $NaHCO_3$ per 1 mg of $NiSO_4 \cdot 6H_2O$.

2. In 1953, Kincaid et al. (360) studied the effect of the chemical agent 2, 3-dimercaptopropanol (BAL, dimercaprol) used in treating nitrogen mustard poisoning on rats receiving different exposures to $Ni(CO)_4$. The experimental data and results are shown in Table 141. They show that BAL increased the LD_{50} of $Ni(CO)_4$ by a factor of approximately two.

The authors noted that:

a) The dosage of BAL given to rats was within the range recommended for administration to humans by Eagle and coworkers (reference in original paper).

b) Their findings differed from those of Barnes and Denz (reference in original paper) who concluded that therapeutic doses were toxic, because Kincaid et al. used much lower dosage levels, 10 mg/kg BW as opposed to 60 to 80 mg/kg BW used by Barnes and Denz. (See also page 146, this Section E3.)

Table 141.

Use of Dimercaprol in Treatment of Nickel Carbonyl Toxicity* (360)

	Control Animals		Treated Animals	
Dose, Mg. per Liter	Exposed	Dead	Exposed	Dead
0.20	18	9	18	0
0.40	9	7	9	3
0.60	9	9	9	8

* All exposures were for 30 minutes. Treatment by intramuscular injection was as follows: day of exposure, 10 mg. of dimercaprol per kilogram of body weight in two doses (0.4 ml. of 0.40% solution of dimercaprol in corn oil); first day after exposure, 8 mg. of dimercaprol per kilogram in two doses; second day after exposure, 3.8 mg. of dimercaprol in two doses of 2.5 and 1.3 mg., and third day after exposure, one dose of 1.3 mg. per kilogram of body weight.

3. In 1963, Jasmin (310) investigated the effect of methandrostenolone on the induction of rhabdomyosarcomas by Ni_3S_2 in rats. It was found that injection s.c. of the steroid accelerated the carcinogenic activity of a single i.m. injection of Ni_3S_2 given to young female Sprague-Dawley rats (100 to 115 g). The incidence of rhabdomyosarcoma was 100% in steroid-treated rats compared with 33% in controls (see Tables 142 and 143 for experimental data and results).

Table 142.

Action of Methandrostenolone on Tumor Development at Site of Injection of Nickel Sulphide (310)

Treatment	Number of rats	Number of rats with tumours	Time of appearance of 1st tumour (days)	Overall average time of appearance (days)	Average progression time* (days)	Survivors after 217 days observation
Nickel sulphide	15	5	149	$176 \cdot 4 \pm 10 \cdot 0$ ($P = 0 \cdot 05$)	$29 \cdot 4 \pm 6 \cdot 2$ ($P < 0 \cdot 05$)	13
Nickel sulphide + methandrostenolone	10	10	137	$157 \pm 4 \cdot 1$	$46 \cdot 2 \pm 3 \cdot 7$	5

* Average time between appearance of 1st tumour and death.

Table 143.

Action of Methandrostenolone Upon Weight of Rhabdomyosarcomas and Distribution of Metastases (310)

Treatment	Number of rats	Number of rats with tumours	Average weight of tumours (g.)	Incidence and distribution of metastases: Lymphatics of pelvic organs	Lymphatics of abdominal wall	Aortic lymph glands	Lungs	Spleen	Heart	Kidney
Nickel sulphide	15	5	$17 \cdot 28 \pm 4 \cdot 2$ ($P < 0 \cdot 1$)	0	0	2	1	0	0	0
Nickel sulphide + methandrostenolone	10	10	$29 \cdot 9 \pm 7 \cdot 4$	2	2	10	8	1	1	1

C. Rabbits

1. In 1926, Bertrand and Mâcheboeuf (061) showed that with certain insulin preparations, the simultaneous injection s.c. of a small quantity (0.01 to 0.05 mg/kg) of Ni (as the chloride) markedly increased the amount of sugar destroyed. The authors concluded that Ni increased the hypoglycemic power of the insulin both in its intensity and duration.

2. In 1927, Labbé et al. (402) confirmed the finding of Bertrand and Mâcheboeuf (061). Rabbits (2.40 kg) fasted for 24 hours and were injected with a convulsive amount of insulin (3 units). The results for one rabbit are shown in Table 144.

Table 144.

Rabbit B (2.40 kg)--3 Clinical Units of Hypodermic Insulin (402)

Glycemia upon fasting . . . 1.19

Hr. Min.	Injection of 3 units of insulin	Insulin: 3 Units + Ni Chloride 0.3 mg.	
1. 0	0.84	0.82	(1)
1. 30	0.66	0.68	
2. 0	0.54	0.57	
2. 40	0.71	0.45	(2)
3. 0	0.77	0.43	
3. 45	0.94	0.54	
5. 0	1.03	0.79	
6. 0	1.06	1.01	

(1) No convulsions with insulin alone.
(2) Convulsions at 2 hours, 30 minutes; 4 hours, 30 minutes.

From the data in Table 144, it can be seen that:

a. With insulin alone, maximum hypoglycemia occurred at the end of two hours with a 51.3/100 reduction.

b. With insulin plus Ni chloride, the maximum occurred at the third hour with a 66/100 reduction.

The authors concluded that the Ni salt increased and prolonged insulin hypoglycemia.

D. Dogs

1. In 1927, Bertrand and Machaboeuf (060) continued their investigations of the effect of Ni salts on the hypoglycemic action of insulin by using a higher species than the rabbit. Two dogs (9.2 kg and 13.3 kg) were injected with three units of the same insulin preparation used with the rabbits (see page , this Section, C1). The same Ni salt solutions were also used as in the previous experiment. The amounts injected are shown in the graphs on page 7 of the original paper.

The results showed that Ni acted with insulin in the same way in dogs as in rabbits, increasing the hypoglycemic action of insulin.

2. In 1928, Magenta (461) obtained results at variance with those of Bertrand and Machebouef (060). A total of 28 dogs, including controls, were fasted for 24 hours and then administered s.c. one-half unit of insulin/kg and 0.01 to 1 mg/kg Ni nitrate i.v. Controls received either insulin or Ni salt.

It was found that:

a. Ni salt alone slightly increased glycemia.

b. Ni salt plus insulin either had a small or no effect on hypoglycemia.

The author concluded that the hypoglycemic effect of insulin was not affected by Ni.

E. Humans

1. In 1926, Bertrand and Machebouef (062) reported on some preliminary experiments in which solutions of 0.1 mg of Ni and CO (as salts) were administered s.c. to diabetics with mixed results. Some showed no improvement while in others certain improvements in diabetic symptoms were observed. When given p.o. (10 g/day) to one elderly diabetic, there was an increased glucide tolerance so that the amount of injected insulin was reduced 25%.

2. In 1927, Serio and Bongiovanni (685) found that with normal and diabetic subjects there was a reduction in glycemia following the injection s.c. of 1 to 2 mg $NiCl_2$. This confirmed the observations of Bertrand and Macheboeuf that Ni salts have a hypoglycemic effect (see page 144, Biochemical Data V).

3. In 1928, Labbé et al. (399) studied whether an intensification of the hypoglycemic effect of insulin would be observed in diabetics treated with a Ni salt and insulin similar to the effect seen in rabbits and dogs (see pages 144, 145, this Section, C1, C2 and D1).

Diabetic patients were administered one-half a clinical unit of insulin/kg BW with either 0.1 mg Ni chloride or 1 mg Ni chloride. The same patients were also tested with insulin alone. No effect was seen on insulin by the addition of Ni salt. (See Tables in original paper.)

The authors postulated that the difference seen between diabetic humans and healthy dogs and rabbits with respect to the strengthening effect of Ni salt on the hypoglycemic action of insulin, might be due to differences in glucide metabolism in healthy animals compared with diabetic humans.

4. In 1954, Sunderman and Kincaid (731) reported on the use of dimercaprol (BAL) therapy in the treatment of 32 persons poisoned by exposure to $Ni(CO)_4$. (All but one survived.) The administration of BAL effected an increased excretion of Ni in urine and a marked decrease in Ni concentration in the blood. The authors believed the BAL was beneficial and even lifesaving. (See also page 142, this Section, B2.)

VI. Consumer Exposure

Schroeder et al. (673) have estimated the average daily intake as 300 to 600 µg on the basis of diet content since some foods such as whole grains, legumes, tea and coffee are high in Ni while fish, meat, milk and eggs are extremely low.

The following amounts of Ni would be provided by a 2300 calorie diet (100 g protein, 250 g carbohydrate and 100 g fat):

a. 3 to 10 µg from meat, milk, eggs, fruit, refined white bread, wheatena, butter and corn oil.

b. 700 to 900 µg from oysters, meat, milk, eggs, oats, whole wheat or rye bread, certain vegetables, potatoes and legumes, with little added fat.

The authors concluded that little has been known of the daily exposure of man to Ni in ordinary foods. They cited data from Underwood (reference in original paper) that on a dry basis, 1.5 to 3.0 ppm were found in lettuce, cabbage, spinach and peas, while wheaten grain, potatoes and fruits contained 0.15 to 0.35 ppm. Kent and McCance (342) estimated that an ordinary diet may supply 0.3 to 0.5 mg Ni/day to an adult.

A number of other souces of Ni exposure have been identified. A few prepared foods have unusually high Ni values apparently from contamination by processing in Ni-plated vessels (Schroeder et al., 673).

The preparation and storage of foods, particularly acidic foods, in Ni utensils may cause a considerable amount of Ni to dissolve in the food (Lehmann also Normann and Hugel, reference in Lich, 433). The average Ni contamination for various foods cooked one hour in contact with a 15% Ni - 18% Cr alloy was 0.06 mg Ni for 4 dm^2 surface in contact with the food (Titus et al., 784). Milk pasteurized in Ni vessels contained 15 ppm Ni, as compared with no Ni in milk pasteurized in glass (Pratt, 607).

The Ni content of commercial beers is usually less than 0.05 ppm (see Tables 145 and 146). If the Ni content is higher than this amount, it indicates that Ni was picked up in the brewery (Stone and Gray, 725).

Table 145.

Typical Nickel Contents of Beers (725)

Brewery	Location	Nickel-ppm
1	U.S. — east	0.04
2	U.S. — east	0.01
3	U.S. — east	0.03
4	U.S. — midwest	0.04
5	U.S. — midwest	0.03
6	U.S. — midwest	0.02
7	U.S. — south	0.02
8	U.S. — west	0.03
9	U.S. — west	0.03
10	U.S. — southwest	0.04
11	Canada	0.04
Beers from breweries stated to use nickel or nickel-alloy equipment		
12	U.S. — east	0.17
13	U.S. — east	0.10
14	U.S. — east	0.04
15	U.S. — east	0.02
16	U.S. — midwest	0.01
17	U.S. — midwest	0.07
18	U.S. — midwest	0.04
19	Canada	1.80
20	Canada	0.44

Table 146.

Nickel Contents of Some Foreign Beers (725)

Brewery	Location	Nickel-ppm
1	Cuba	0.01
2	Denmark	0.01
3	England	0.01
4	Malta	0.02
5	Mexico	0.03
6	Norway	0.01
7	Venezuela	0.06

Ni was also found to be widely distributed in the air from all of a group of American cities studied, with significant quantities detected in 90.7% of samples. The extreme ranges were 0.005 $\mu g/m^3$ in suburban Houston to 0.2 $\mu g/m^3$ in East St. Louis and New York (Tabor and Warren reference in Schroeder et al., 673). It was inferred from the absence of Ni in local snow that urban Ni comes from industrial contaminants with a small amount from motor vehicle exhausts. At a respiratory volume of 15 m^3/day, the estimated amount inspired in cities was 0.075 to 3.0 µg (less than 0.3 µg in two-thirds of the studied cities) provided exposures were continuous (Schroeder et al., 673). According to these researchers, exposure to Ni via air represents a "very small increment of the total daily intake". However, they pointed out that if Ni in air were deposited in lung in an insoluble form at the rate of 10 µg/year, it could be responsible for the accumulation of 0.4 mg in lung.

Nickel sulfate is used as a mineral supplement at levels of up to one mg Ni/day (192).

Mastromatteo (479) reported that the significance of residues of metallic Ni in food from its use as a catalyst in the hydrogenation of fats and oils, has been raised. Stewart and Ross (722) found that Ni accumulated in apple fruit after a single spray of $NiCl_2$ (see Figure 20). Harvest residues for the year 1964, 1965, 1967 were 125, 147 and 199 µg/10 apples respectively.

Sunderman and Sunderman (730) determined the Ni content in six different cigarette brands (see Table 147). They estimated that a person inhaling the main-stream smoke from two cigarette packs/day for one year would inhale 5400 µg Ni, an amount three times the amount found to be carcinogenic to rats. Concentrations of about 140 ppb Ni were found in the main-stream cigarette smoke. The authors considered this fact to indicate that "efforts should be made to eliminate Ni vapors from tobacco smoke".

The water supply may provide another source of Ni. Itskova et al. (303) expressed concern about consumer exposure in Russia to "abnormal amounts" of Ni in their water supply from two main sources; metal processing and Ni-rich soil. Effluent guidelines and standards established by the U. S. Environmental Protection Agency (EPA) for the electroplating industry were published in the Federal Register on March 28, 1974 (012). The effluent limitations are given in the tables.

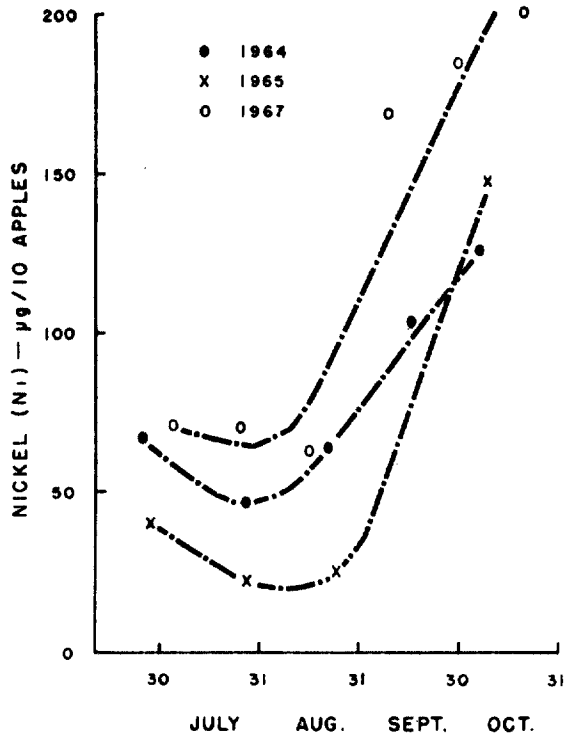

Figure 20. Nickel Residues in Apple Fruit Following A Single Spray of Nickel Chloride (722)

Table 147.

Nickel in 6 Brands of Cigarettes (730)

Ni (µg.) per Cigarette					
A	B	C	D	E	F (Filter)
1.50	1.75	1.85	2.30	2.48	3.07
Mean = 1.99					

The Office of Air and Water Programs of the EPA has analyzed water supply systems throughout the United States for the presence of various metals including Ni. Out of the total of 9169 values stored in their computer, 4977 show the presence of Ni in amounts ranging from 0.001 to 1.3 mg/liter. Table 150 shows the number of samples with a Ni content ranging from zero to three times the drinking water standards limit for Ni.

The drinking water standards limit for Ni has not been officially set. In January 1974, R. G. Tardiff, CDB, WSRL sent a communication (766) to Gary Hutchinson, Chief WSP, Region IV, which is quoted in full in the following paragraphs and which has a recommended guideline for such a standard. This is, at present, the one being followed.

Table 148 (012)

Effluent characteristic	Effluent limitations: Maximum for any 1 day	Effluent limitations: Average of daily values for 30 consecutive days shall not exceed—
	Metric units (milligrams per square meters per operation)	
Cu	80	40
Ni	80	40
CrVI	8	4
Cr, total	80	40
Zn	80	40
CN, A	8	4
CN, total	80	40
TSS	2,400	1,600
pH	Within the range 6.0 to 9.5.	
	English units (pounds per million square feet per operation).	
Cu	16.4	8.2
Ni	16.4	8.2
CrVI	1.6	.8
Cr, total	16.4	8.2
Zn	16.4	8.2
CN, A	1.6	.8
CN, total	16.2	8.7
TSS	491.0	327.0
pH	Within the range 6.0 to 9.5.	

Table 149 (012)

Effluent characteristic	Effluent limitations: Maximum for any 1 day	Effluent limitations: Average of daily values for 30 consecutive days shall not exceed—
	Metric units (milligrams per square meters per operation)	
Cu	160	80
Ni	160	80
CrVI	16	8
Cr, total	160	80
Zn	160	80
CN, A	16	8
CN, total	160	80
TSS	4,800	3,200
pH	Within the range 6.0 to 9.5.	
	English units (pounds per million square feet per operation)	
Cu	32.7	16.4
Ni	32.7	16.4
CrVI	3.3	1.6
Cr, total	32.7	16.4
Zn	32.7	16.4
CN, A	3.3	1.6
CN, total	32.7	16.4
TSS	982.0	654.0
pH	Within the range 6.0 to 9.5.	

The Communication reads as follows:

"The urgency of your need to have a guideline for nickel in drinking water has prompted me to make an evaluation and recommendation based upon the National Academy of Sciences recommendation to the National Aeronautics and Space Administration for manned space flights. The maximum allowable limit recommended for the long-term flights (i.e., 3 years) is 0.05 mg/l. The standard is based in part on the fact that the astronauts are very healthy individuals, and do not reflect the general public with respect to susceptibility to the toxic effects of chemical agents (that is, they are expected to be slightly less susceptible than the general population and much less susceptible than special groups within the population.

In order to take into account the differences in individual susceptibilities, the limit could be lowered by one order of magnitude with assurance that a limit of 0.005 mg/l is reasonably safe. Newer information about the biological effects of nickel suggest that the above guidelines for Ni may be too conservative; however, until this newer information is fully evaluated, this limit of 5 µg/l should be applied for nickel in potable water."

Table 150

The following Frequency Table (341) was prepared by the Basic Data Unit, Water Supply Division of the Environmental Protection Agency (EPA) for this monograph. This table contains the results of analyses for nickel in water supply systems in the United States made between 1969 and 1974 along with a national total. Specifically, this table gives the number of samples ranging from zero to three times the drinking water standards limit of 0.005 mg/liter (see recommended guideline for nickel in drinking water).

In the table, S = Surface Water Systems; G = Ground Water Systems, and C = Combined Systems. The line of decimal numbers across the top of the page represents the percentage of the limit (the last number 70.01500 = 3 times the limit).

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
ALABAMA															
S	0	34	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	17	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	107	0	0	0	0	0	0	0	0	0	0	0	0	0
ALASKA															
S	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
ARIZONA															
S	0	14	0	0	0	0	0	0	0	0	0	0	0	0	1
G	0	32	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
ARKANSAS															
S	0	4	0	1	0	0	0	0	0	0	0	0	0	0	0
G	0	4	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
CALIFORNIA															
S	0	166	0	5	0	0	0	0	0	0	0	0	0	0	1
G	0	350	0	42	0	0	0	0	0	0	0	0	0	0	15
C	0	17	0	4	0	0	0	0	0	0	0	0	0	0	0
COLORADO															
S	0	49	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	57	0	1	0	0	0	0	0	0	0	0	0	0	13
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
CONNECTICUT															
S	0	192	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	174	0	0	0	0	0	0	0	0	0	0	0	0	2
C	0	18	0	0	0	0	0	0	0	0	0	0	0	0	0

FREQUENCY TABLES
FOR ALL SUPPLIES
05/31/74

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
DELAWARE															
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
WASHINGTON D.C.															
S	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
FLORIDA															
S	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	113	0	0	0	0	0	0	0	0	0	0	0	0	6
C	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0
GEORGIA															
S	0	12	0	1	0	0	0	0	0	0	0	0	0	0	0
G	0	294	0	31	0	0	0	0	0	0	0	0	0	0	6
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
HAWAII															
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
IDAHO															
S	0	21	8	0	0	0	0	0	0	0	0	0	0	0	0
G	0	106	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
ILLINOIS															
S	0	141	0	0	0	0	0	0	0	0	0	0	0	0	6
G	0	58	0	1	0	0	0	0	0	0	0	0	0	0	1
C	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
INDIANA															
S	0	15	0	0	0	0	0	0	0	0	0	0	0	0	1
G	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
IOWA															
S	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	5	0	0	0	0	0	0	0	0	0	0	0	0	2
C	0	2	0	0	0	0	0	0	0	0	0	0	0	0	1
KANSAS															
S	0	26	0	1	0	0	0	0	0	0	0	0	0	0	3
G	0	162	0	0	0	0	0	0	0	0	0	0	0	0	10
C	0	48	0	1	0	0	0	0	0	0	0	0	0	0	3
KENTUCKY															
S	0	169	0	4	0	0	0	0	0	0	0	0	0	0	3
G	0	211	0	3	0	0	0	0	0	0	0	0	0	0	20
C	0	13	0	1	0	0	0	0	0	0	0	0	0	0	0
LOUISIANA															
S	0	78	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	43	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MAINE															
S	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	783	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MARYLAND															
S	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	24	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
MASSACHUSETTS															
S	0	897	0	0	0	0	0	0	0	0	0	0	0	0	4
G	0	46	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0
MICHIGAN															
S	0	26	0	1	0	0	0	0	0	0	0	0	0	0	0
G	0	3	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
MINNESOTA															
S	0	38	0	1	0	0	0	0	0	0	0	0	0	0	1
G	0	52	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0
MISSISSIPPI															
S	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	26	0	1	0	0	0	0	0	0	0	0	0	0	15
C	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
MISSOURI															
S	0	343	0	4	0	0	0	0	0	0	0	0	0	0	1
G	0	75	0	2	0	0	0	0	0	0	0	0	0	0	5
C	0	3	0	2	0	0	0	0	0	0	0	0	0	0	0
MONTANA															
S	0	11	0	1	0	0	0	0	0	0	0	0	0	0	2
G	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	2	0	0	0	0	0	0	0	0	0	0	0	0	3
NEBRASKA															
S	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	10	0	0	0	0	0	0	0	0	0	0	0	0	5
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
NEVADA															
S	0	8	0	0	0	0	0	0	0	0	0	0	0	0	2
G	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NEW HAMPSHIRE															
S	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
NEW JERSEY															
S	0	53	0	0	0	0	0	0	0	0	0	0	0	0	2
G	0	83	0	1	0	0	0	0	0	0	0	0	0	0	6
C	0	17	0	0	0	0	0	0	0	0	0	0	0	0	0
NEW MEXICO															
S	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	61	0	3	0	0	0	0	0	0	0	0	0	0	1
C	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
NEW YORK															
S	0	110	0	16	0	0	0	0	0	0	0	0	0	0	4
G	0	278	0	10	0	0	0	0	0	0	0	0	0	0	29
C	0	11	0	1	0	0	0	0	0	0	0	0	0	0	0
NORTH CAROLINA															
S	0	94	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	31	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
NORTH DAKOTA															
S	0	55	0	0	0	0	0	0	0	0	0	0	0	0	1
G	0	45	0	3	0	0	0	0	0	0	0	0	0	0	0
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
OHIO															
S	0	158	0	3	0	0	0	0	0	0	0	0	0	0	7
G	0	60	0	3	0	0	0	0	0	0	0	0	0	0	5
C	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0
OKLAHOMA															
S	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
OREGON															
S	0	26	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	345	0	1	0	0	0	0	0	0	0	0	0	0	5
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PENNSYLVANIA															
S	0	16	0	1	0	0	0	0	0	0	0	0	0	0	3
G	0	15	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
RHODE ISLAND															
S	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SOUTH CAROLINA															
S	0	13	0	3	0	0	0	0	0	0	0	0	0	0	0
G	0	30	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SOUTH DAKOTA															
S	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
TENNESSEE															
S	0	79	0	2	0	0	0	0	0	0	0	0	0	0	1
G	0	316	0	3	0	0	0	0	0	0	0	0	0	0	24
C	0	7	0	0	0	0	0	0	0	0	0	0	0	0	1
TEXAS															
S	0	9	0	0	0	0	0	0	0	0	0	0	0	0	3
G	0	12	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UTAH															
S	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	2	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VERMONT															
S	0	126	0	1	0	0	0	0	0	0	0	0	0	0	5
G	0	169	0	3	0	0	0	0	0	0	0	0	0	0	26
C	0	37	0	0	0	0	0	0	0	0	0	0	0	0	1
VIRGINIA															
S	0	17	0	2	0	0	0	0	0	0	0	0	0	0	1
G	0	128	0	1	0	0	0	0	0	0	0	0	0	0	0
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
WASHINGTON															
S	0	61	0	0	0	0	0	0	0	0	0	0	0	0	8
G	0	21	0	0	0	0	0	0	0	0	0	0	0	0	0
C	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
WEST VIRGINIA															
S	0	40	0	4	0	0	0	0	0	0	0	0	0	0	0
G	0	32	0	2	0	0	0	0	0	0	0	0	0	0	2
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

FREQUENCY TABLES
FOR ALL SUPPLIES
05/31/74

NICKEL(0.0050)

	<0	0	0.00050	0.00100	0.00150	0.00200	0.00250	0.00300	0.00350	0.00400	0.00450	0.00500	0.01000	0.01500	>0.01500
WISCONSIN															
S	0	18	0	0	0	0	0	0	0	0	0	0	0	0	5
G	0	19	0	0	0	0	0	0	0	0	0	0	0	0	3
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
WYOMING															
S	0	47	0	5	0	0	0	0	0	0	0	0	0	0	0
G	0	257	0	0	0	0	0	0	0	0	0	0	0	0	8
C	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0
PUERTO RICO															
S	0	14	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	2	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
VIRGIN ISLANDS															
S	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
G	0	4	0	0	0	0	0	0	0	0	0	0	0	0	1
C	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
NATIONAL TOTAL															
S	0	3229	8	56	0	0	0	0	0	0	0	0	0	0	57
G	0	4591	0	116	0	0	0	0	0	0	0	0	0	0	215
C	0	345	0	10	0	0	0	0	0	0	0	0	0	0	10

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